NOVEL 2,4,6-TRI-SUBSTITUTED HETEROCYCLES AND USES THEREOF

This application claims the benefit of U.S. Provisional Application No. 60/484,250 filed on June 30, 2003.

Field of the invention

The present invention relates to novel triazines, pyrimidines, and pyridines and their pharmaceutical compositions and methods of use. In addition, the present invention relates to therapeutic methods for the treatment and prevention of various diseases especially Alzheimer's disease and other diseases relating to the deposition of amyloid.

Background of the invention

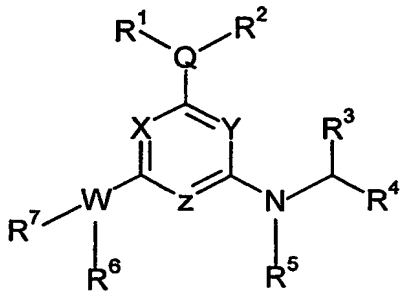
Alzheimer's Disease (AD) is a progressive, neurodegenerative disease characterized clinically by progressive loss of memory, cognition, reasoning, judgment and emotional stability. AD is a common cause of dementia in humans and a leading cause of death in the United States. AD has been observed in races and ethnic groups worldwide and presents a major public health problem throughout the world. No treatment that effectively prevents AD or reverses the clinical symptoms and underlying pathophysiology is currently available and the disease is currently considered among experts to be incurable.

The histopathological manifestations of AD are characteristic lesions known as amyloid (or senile) plaques and neurofibrillar tangles that are found in the regions of the brain associated with memory, reasoning and cognition. Similar alterations are observed in patients with Trisomy 21 (Down's syndrome) and hereditary cerebral hemorrhage with amyloidosis of the Dutch-type.

The major constituent of amyloid plaques is amyloid β protein. Amyloid β protein is derived from the proteolytic cleavage of amyloid precursor protein (APP). Processing of APP to amyloid β protein and other APP fragments is governed by a group of enzymes known as secretases. One type of secretase, γ-secretase, is responsible for the protein cleavage that produces amyloid β protein. Compounds that inhibit either β or γ secretase activity, either directly or indirectly would reduce the production of amyloid β protein resulting in the treatment or prevention of disorders associated with amyloid β protein. Thus there is a continuing need for compounds that inhibit amyloid β protein production. The present invention meets this and related needs by providing a family of novel compounds and related methods of use.

Summary of the invention

One embodiment of the invention is a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

Q is C, CH or N;

W is N or S, when W is S, R^6 is not present;

X is C or N, provided that when Y and Z are C, X is N;

Y is C or N, provided that when X and Z are C, Y is N;

Z is C or N, provided that when X and Y are C, Z is N;

R^1 and R^2 are at each occurrence independently selected from H, CH_3, optionally substituted C_{1-6}alkyl, optionally substituted carbocycle, or optionally substituted heterocycle; or R^1 and R^2 in combination can form an optionally substituted heterocycle, or an optionally substituted carbocycle;

R^3 is selected from H, or optionally substituted C_{1-6}alkyl;

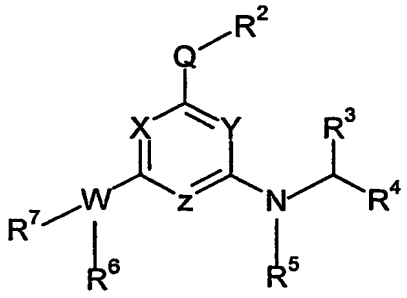
R^4 is selected from H, optionally substituted C_{1-6}alkyl, $-C(=O)OCH_3$, optionally substituted carbocycle, $-C(=O)NH(CH_2)$heterocycle, or $-C(=O)NH(CH_2)CH_3$;

R^5 is selected from H, or CH_3;

R^6 is selected from H;

R^7 is selected from optionally substituted carbocycle.

A further embodiment is a compound of formula (II) or a pharmaceutically acceptable salt thereof:



(II)

wherein:

Q is O, S, SO or SO_2;

W is N or halogen, when W is halogen neither R^6 nor R^7 are present;

X is C or N, provided that when Y and Z are C, X is N;

Y is C or N, provided that when X and Z are C, Y is N;

Z is C or N, provided that when X and Y are C, Z is N;

R^2 is selected from H, optionally substituted C_{1-6}alkyl, optionally substituted carbocycle, or optionally substituted heterocycle;

R^3 is selected from H, or optionally substituted C_{1-6}alkyl;

R^4 is selected from H, optionally substituted C_{1-6}alkyl, optionally substituted heterocycle, cyano, $-C(=O)OCH_3$, $-C(=O)OCH_3$, $-C(=O)NH_2$, -C(=O)NH-optionally substituted C_{1-6}alkyl, $-C(=O)NH(CH_2)_{0-3}$-optionally substituted carbocycle, $-C(=O)NH(CH_2)_{0-3}$-optionally substituted heterocycle, $-C(=O)NH(CH_2)_{1-3}N(CH_3)_2$, $C(=O)NH(CH_2)_{1-3}C(OCH_3)_2$, $C(=O)NH(CH_2)_{1-3}NHC(=O)OC(CH_3)_3$, $-C(=O)NH(CH_2)_{1-3}O(CH_2)_{1-3}OH$, -C(=O)-optionally substituted heterocycle, $-C(=O)NH(CH_2)_{1-3}C(=O)OCH_3$, $-C(=O)NH(CH_2)_{1-3}OC(CH_3)_3$, $-C(=O)NH(CH_2)_{1-3}SCH_3$, or $C(=O)NH(CH_2)_{1-3}C(=O)OH$;

R^5 is selected from H, or CH_3;

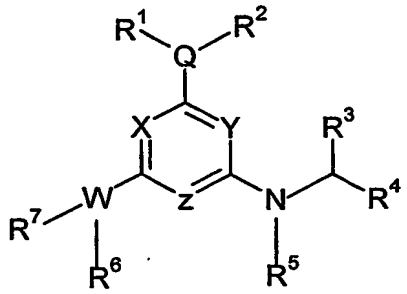
R^4 and R^5 in combination form an optionally substituted heterocycle;

R^6 is selected from H or CH_3;

R^7 is selected from optionally substituted C_{1-6}alkyl, optionally substituted carbocycle, optionally substituted heterocycle, or $-(CH_2)_{1-3}$-optionally substituted carbocycle.

Detailed description of the invention

One embodiment of the invention is a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

Q is C, CH or N;

W is N or S, when W is S, R^6 is not present;

X is C or N, provided that when Y and Z are C, X is N;

Y is C or N, provided that when X and Z are C, Y is N;

Z is C or N, provided that when X and Y are C, Z is N;

R^1 and R^2 are at each occurrence independently selected from H, CH_3, optionally substituted C_{1-6}alkyl, optionally substituted carbocycle, or optionally substituted heterocycle; or R^1 and R^2 in combination can form an optionally substituted heterocycle, or an optionally substituted carbocycle;

R^3 is selected from H, or optionally substituted C_{1-6}alkyl;

R^4 is selected from H, optionally substituted C_{1-6}alkyl, -C(=O)OCH_3, optionally substituted carbocycle, -C(=O)NH(CH_2)heterocycle, or -C(=O)NH(CH_2)CH_3;

R^5 is selected from H, or CH_3;

R^6 is selected from H;

R^7 is selected from optionally substituted carbocycle.

A further embodiment is a compound of claim 1, wherein:

Q is N.

A further embodiment is a compound of claim 1, wherein:

W is S, and R^6 is not present.

A further embodiment is a compound of claim 1, wherein:

X is C.

A further embodiment is a compound of claim 1, wherein:

Y is N.

A further embodiment is a compound of claim 1, wherein:

Z is N.

A further embodiment is a compound of claim 1, wherein:

R^1 and R^2 are at each occurrence are independently selected from H, or optionally substituted carbocycle, or optionally substituted heterocycle.

A compound of claim 1, wherein:

R^3 is an optionally substituted C_{1-6}alkyl.

A further embodiment is a compound of claim 1, wherein:

R^4 is -C(=O)NH(CH_2)heterocycle.

A further embodiment is a compound of claim 1, wherein:

R^5 is selected from H.

A further embodiment is a compound of claim 1, wherein:

R^7 is an optionally substituted carbocycle.

A further embodiment is a compound of claim 1, wherein:

Q is N or C;

W is S, and R^6 is not present;

X is C or N, provided that when Y and Z are C, X is N;

Y is C or N, provided that when X and Z are C, Y is N;

Z is C or N, provided that when X and Y are C, Z is N;

R^1 and R^2 are at each occurrence independently selected from H, or optionally substituted carbocycle; or optionally substituted heterocycle or optionally substituted C_{1-6}alkyl;

R^3 is selected from H, or optionally substituted C_{1-6}alkyl;

R^4 is selected from H, -C(=O)NH(CH_2)heterocycle or optionally substituted carbocycle;

R^5 is selected from H;

R^7 is selected from optionally substituted carbocycle.

A further embodiment is a compound of claim 1, wherein:

Q is N or C;

W is S, and R^6 is not present;

X is C or N, provided that when Y and Z are C, X is N;

Y is C or N, provided that when X and Z are C, Y is N;

Z is C or N, provided that when X and Y are C, Z is N;

R^1 and R^2 are at each occurrence independently selected from H, or optionally substituted carbocycle; or optionally substituted heterocycle or optionally substituted C_{1-6}alkyl;

R^3 is selected from H, or optionally substituted C_{1-6}alkyl;

R^4 is selected from H, or -C(=O)NH(CH_2)heterocycle;

R^5 is selected from H;

R^7 is selected from optionally substituted carbocycle.

A further embodiment is a compound of claim 1, wherein:

Q is N or C;

W is S, and R^6 is not present;

X is C or N, provided that when Y and Z are C, X is N;

Y is C or N, provided that when X and Z are C, Y is N;

Z is C or N, provided that when X and Y are C, Z is N;

R^1 and R^2 are at each occurrence independently selected from H, or optionally substituted carbocycle; or optionally substituted heterocycle;

R^3 is selected from H, or optionally substituted C_{1-6}alkyl;

R^4 is selected from H, -C(=O)NH(CH_2)heterocycle;

R^5 is selected from H;

R^7 is selected from optionally substituted carbocycle.

A further embodiment is a compound of claim 1, wherein:

Q is N or C;

W is S, and R^6 is not present;

X is C or N;

Y is N;

Z is N;

R^1 and R^2 are at each occurrence independently selected from H, or optionally substituted carbocycle; or optionally substituted heterocycle;

R^3 is selected from H, or optionally substituted C_{1-6}alkyl;

R^4 is selected from H, -C(=O)NH(CH_2)heterocycle;

R^5 is selected from H;

R^7 is selected from optionally substituted carbocycle.

A further embodiment is a compound of claim 1, wherein:

Q is N;

W is S, and R^6 is not present;

X is C or N;

Y is N;

Z is N;

R^1 and R^2 are at each occurrence independently selected from H, or optionally substituted carbocycle; or optionally substituted heterocycle;

R^3 is selected from H, or optionally substituted C_{1-6}alkyl;

R^4 is selected from H, -C(=O)NH(CH_2)heterocycle;

R^5 is selected from H;

R^7 is selected from optionally substituted carbocycle.

A further embodiment is a compound of claim 1, wherein:

Q is N;

W is S, and R^6 is not present;

X is C;

Y is N;

Z is N;

R^1 and R^2 are at each occurrence independently selected from H, or optionally substituted carbocycle; or optionally substituted heterocycle;

R^3 is selected from H, or optionally substituted C_{1-6}alkyl;

R^4 is selected from H, -C(=O)NH(CH_2)heterocycle;

R^5 is selected from H;

R^7 is selected from optionally substituted carbocycle.

A further embodiment is a compound of formula (I) selected from:

Methyl N-{4-[(3-fluorophenyl)amino]-6-[(2-hydroxypropyl)amino]-1,3,5-triazin-2-yl}-L-leucinate;

Methyl N-{4-[(3-fluorophenyl)amino]-6-morpholin-4-yl-1,3,5-triazin-2-yl}-L-leucinate;

(2R)-2-({4-[(3-fluorophenyl)amino]-6-[(3-methoxypropyl)amino]-1,3,5-triazin-2-yl}amino)-4-methylpentan-1-ol;

Methyl N-{4-[(3-fluorophenyl)amino]-6-[(4-methoxybenzyl)amino]-1,3,5-triazin-2-yl}-D-leucinate;

Methyl N-{4-[(cyclopropylmethyl)amino]-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-D-leucinate;

Methyl N-{4-[(3-fluorophenyl)amino]-6-[(3-methoxypropyl)amino]-1,3,5-triazin-2-yl}-D-leucinate;

(2R)-2-({4-[(cyclopropylmethyl)amino]-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}amino)-4-methylpentan-1-ol;

Methyl N-{4-[(3-fluorophenyl)amino]-6-[(tetrahydrofuran-2-ylmethyl)amino]-1,3,5-triazin-2-yl}-L-leucinate;

Methyl N-(4-[(3-fluorophenyl)amino]-6-{[3-(1H-imidazol-1-yl)propyl]amino}-1,3,5-triazin-2-yl)-L-leucinate;

Methyl N-{4-[(2-anilinoethyl)amino]-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-L-leucinate;

Methyl N-{4-[(3-fluorophenyl)amino]-6-[(2-hydroxy-2-phenylethyl)amino]-1,3,5-triazin-2-yl}-L-leucinate;

Methyl N-(4-[(3-fluorophenyl)amino]-6-{[2-(4-methoxyphenyl)ethyl]amino}-1,3,5-triazin-2-yl)-L-leucinate;

Methyl N-{4-[(2,3-dihydroxypropyl)amino]-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-L-leucinate;

Methyl N-[4-[(3-fluorophenyl)amino]-6-(3-hydroxypyrrolidin-1-yl)-1,3,5-triazin-2-yl]-L-leucinate;

Methyl N-{4-[(2-amino-2-oxoethyl)(methyl)amino]-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-L-leucinate;

(2R)-2-[(4-[(3-fluorophenyl)amino]-6-{[2-(4-methoxyphenyl)ethyl]amino}-1,3,5-triazin-2-yl)amino]-4-methylpentan-1-ol;

Methyl N-{4-[(2-cyanoethyl)(methyl)amino]-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-L-leucinate;

Methyl N-[4-[(3-fluorophenyl)amino]-6-(4-pyridin-4-ylpiperazin-1-yl)-1,3,5-triazin-2-yl]-L-leucinate;

Methyl N-{4-(4-cyano-4-phenylpiperidin-1-yl)-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-L-leucinate;

Methyl N-{4-[(3-fluorophenyl)amino]-6-[(3-hydroxy-2,2-dimethylpropyl)amino]-1,3,5-triazin-2-yl}-L-leucinate;

Methyl N-{4-[(3-fluorophenyl)amino]-6-[(3-morpholin-4-ylpropyl)amino]-1,3,5-triazin-2-yl}-L-leucinate;

Methyl N-{4-({2-[4-(aminosulfonyl)phenyl]ethyl}amino)-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-L-leucinate;

Methyl N-{4-{[2-(dimethylamino)ethyl]amino}-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-L-leucinate;

Methyl N-(4-[(3-fluorophenyl)amino]-6-{[2-(2-hydroxyethoxy)ethyl]amino}-1,3,5-triazin-2-yl)-L-leucinate;

Methyl N-{4-[(3-fluorophenyl)amino]-6-[(4-hydroxybutyl)amino]-1,3,5-triazin-2-yl}-L-leucinate;

Methyl N-(4-[(3-fluorophenyl)amino]-6-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}-1,3,5-triazin-2-yl)-L-leucinate;

Methyl N-[4-[(3-fluorophenyl)amino]-6-(4-methoxyphenyl)-1,3,5-triazin-2-yl]-L-leucinate;

Methyl N-[4-[(3-fluorophenyl)amino]-6-(4-methoxybenzyl)-1,3,5-triazin-2-yl]-D-leucinate;

Methyl N-[4-[(3-fluorophenyl)amino]-6-(4-methoxybenzyl)-1,3,5-triazin-2-yl]glycinate;

(2S)-2-{[4-[(3-fluorophenyl)amino]-6-(4-methoxybenzyl)-1,3,5-triazin-2-yl]amino}-4-methylpentan-1-ol;

N^2-Benzyl-N^4-(3-fluorophenyl)-6-(4-methoxybenzyl)-1,3,5-triazine-2,4-diamine;

N^2-{4-[(5-fluoro-2-methylphenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-(tetrahydrofuran-2-ylmethyl)-L-leucinamide;

N^2-{4-[(5-fluoro-2-methylphenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-propyl-L-leucinamide;

N^2-{4-[(3-cyanophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-(tetrahydrofuran-2-ylmethyl)-L-leucinamide;

N^2-{4-[(5-Chloro-2-methylphenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-(tetrahydrofuran-2-ylmethyl)-L-leucinamide;

N^2-{4-[(3,5-Difluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-(tetrahydrofuran-2-ylmethyl)-L-leucinamide;

Methyl N-[4-[(3-fluorophenyl)amino]-6-(4-methoxybenzyl)pyrimidin-2-yl]-L-leucinate;

Methyl N-[2-[(3-fluorophenyl)amino]-6-(4-methoxybenzyl)pyrimidin-4-yl]-L-leucinate;

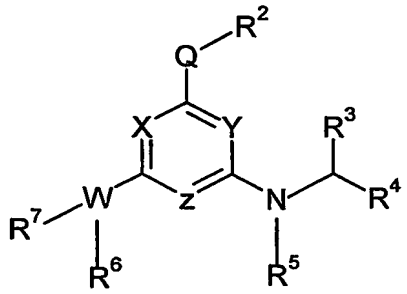
(S)-2-[4-(3-Fluoro-phenylamino)-6-(4-methoxy-phenylsulfanyl)-1-oxy-pyridin-2-ylamino]-4-methyl-pentanoic acid methyl ester;

2-[6-(3-Fluoro-phenylamino)-2-(4-methoxy-phenylsulfanyl)-pyrimidin-4-ylamino]-4-methyl-pentanoic acid methyl ester;

(S)-2-[4-(3-Cyano-phenylamino)-6-(quinolin-8-ylsulfanyl)-pyrimidin-2-ylmethyl]-4-methyl-pentanoic acid (tetrahydro-furan-2-ylmethyl)-amide;

(S)-2-[4-(4-Amino-phenylsulfanyl)-6-(3-cyano-phenylamino)-pyrimidin-2-ylmethyl]-4-methyl-pentanoic acid (tetrahydro-furan-2-ylmethyl)-amide;

A further embodiment is a compound of formula (II) or a pharmaceutically acceptable salt thereof:



(II)

wherein:

Q is O, S, SO or SO_2;

W is N or halogen, when W is halogen neither R^6 nor R^7 are present;

X is C or N, provided that when Y and Z are C, X is N;

Y is C or N, provided that when X and Z are C, Y is N;

Z is C or N, provided that when X and Y are C, Z is N;

R^2 is selected from H, optionally substituted C_{1-6}alkyl, optionally substituted carbocycle, or optionally substituted heterocycle;

R^3 is selected from H, or optionally substituted C_{1-6}alkyl;

R^4 is selected from H, optionally substituted C_{1-6}alkyl, optionally substituted heterocycle, cyano, $-C(=O)OCH_3$, $-C(=O)OCH_3$, $-C(=O)NH_2$, -C(=O)NH-optionally

substituted C_{1-6}alkyl, -C(=O)NH$(CH_2)_{0-3}$-optionally substituted carbocycle, -C(=O)NH$(CH_2)_{0-3}$-optionally substituted heterocycle, -C(=O)NH$(CH_2)_{1-3}N(CH_3)_2$, C(=O)NH$(CH_2)_{1-3}C(OCH_3)_2$, C(=O)NH$(CH_2)_{1-3}$NHC(=O)O$C(CH_3)_3$, -C(=O)NH$(CH_2)_{1-3}O(CH_2)_{1-3}$OH, -C(=O)-optionally substituted heterocycle, -C(=O)NH$(CH_2)_{1-3}$C(=O)OCH_3, -C(=O)NH$(CH_2)_{1-3}OC(CH_3)_3$, -C(=O)NH$(CH_2)_{1-3}SCH_3$, or C(=O)NH$(CH_2)_{1-3}$C(=O)OH;

R^5 is selected from H, or CH_3;

R^4 and R^5 in combination form an optionally substituted heterocycle;

R^6 is selected from H or CH_3;

R^7 is selected from optionally substituted C_{1-6}alkyl, optionally substituted carbocycle, optionally substituted heterocycle, or -$(CH_2)_{1-3}$-optionally substituted carbocycle.

A further embodiment is a compound of formula (II), wherein:

Q is S;

A further embodiment is a compound of formula (II), wherein:

W is N;

A further embodiment is a compound of formula (II), wherein:

X is N;

A further embodiment is a compound of formula (II), wherein:

X is C;

A further embodiment is a compound of formula (II), wherein:

Y is N;

A further embodiment is a compound of formula (II), wherein:

Y is C.

A further embodiment is a compound of formula (II), wherein:

Z is N.

A further embodiment is a compound of formula (II), wherein:

Z is C.

A further embodiment is a compound of formula (II), wherein:

R^2 is optionally substituted carbocycle.

A further embodiment is a compound of formula (II), wherein:

R^3 is optionally substituted C_{1-6}alkyl.

A further embodiment is a compound of formula (II), wherein:

R^4 is selected from, -C(=O)OCH_3, -C(=O)-optionally substituted heterocycle, -C(=O)NH$(CH_2)_{0-3}$-optionally substituted heterocycle, or -C(=O)NH$(CH_2)_{1-3}SCH_3$.

A further embodiment is a compound of formula (II), wherein:

R^5 is selected from H, or CH_3;

A further embodiment is a compound of formula (II), wherein:

R^6 is selected from H or CH_3;

A further embodiment is a compound of formula (II), wherein:

R^7 is optionally substituted carbocycle.

A further embodiment is a compound of formula (II):

wherein:

Q is S, SO or SO_2;

W is N;

X is C or N, provided that when Y and Z are C, X is N;

Y is C or N, provided that when X and Z are C, Y is N;

Z is C or N, provided that when X and Y are C, Z is N;

R^2 is selected from H, optionally substituted carbocycle, or optionally substituted heterocycle;

R^3 is optionally substituted C_{1-6}alkyl;

R^4 is selected from, $-C(=O)OCH_3$, -C(=O)-optionally substituted heterocycle, $-C(=O)NH(CH_2)_{0-3}$-optionally substituted heterocycle, $-C(=O)NH(CH_2)_{1-3}SCH_3$, optionally substituted heterocycle, cyano, $-C(=O)NH_2$, -C(=O)NH-optionally substituted C_{1-6}alkyl, $-C(=O)NH(CH_2)_{0-3}$-optionally substituted carbocycle, $-C(=O)NH(CH_2)_{1-3}N(CH_3)_2$, $C(=O)NH(CH_2)_{1-3}C(OCH_3)_2$, $C(=O)NH(CH_2)_{1-3}NHC(=O)OC(CH_3)_3$, $-C(=O)NH(CH_2)_{1-3}O(CH_2)_{1-3}OH$, -, $-C(=O)NH(CH_2)_{1-3}C(=O)OCH_3$, $-C(=O)NH(CH_2)_{1-3}OC(CH_3)_3$, or $C(=O)NH(CH_2)_{1-3}C(=O)OH$;

R^5 is H;

R^4 and R^5 in combination form an optionally substituted heterocycle;

R^6 is selected from H;

R^7 is selected from, optionally substituted carbocycle, optionally substituted heterocycle, or $-(CH_2)_{1-3}$-optionally substituted carbocycle.

A further embodiment is a compound of formula (II):

wherein:

Q is S;

W is N;

X is C or N, provided that when Y and Z are C, X is N;

Y is C or N, provided that when X and Z are C, Y is N;

Z is C or N, provided that when X and Y are C, Z is N;

R^2 is selected from H, optionally substituted carbocycle, or optionally substituted heterocycle;

R^3 is optionally substituted C_{1-6}alkyl;

R^4 is selected from, $-C(=O)OCH_3$, -C(=O)-optionally substituted heterocycle, $-C(=O)NH(CH_2)_{0-3}$-optionally substituted heterocycle, $-C(=O)NH(CH_2)_{1-3}SCH_3$, heterocycle, cyano, $-C(=O)NH_2$, -C(=O)NH-optionally substituted C_{1-6}alkyl, $-C(=O)NH(CH_2)_{0-3}$-optionally substituted carbocycle, $-C(=O)NH(CH_2)_{1-3}N(CH_3)_2$, $C(=O)NH(CH_2)_{1-3}C(OCH_3)_2$, $C(=O)NH(CH_2)_{1-3}NHC(=O)OC(CH_3)_3$, $-C(=O)NH(CH_2)_{1-3}O(CH_2)_{1-3}OH$, -, $-C(=O)NH(CH_2)_{1-3}C(=O)OCH_3$, $-C(=O)NH(CH_2)_{1-3}OC(CH_3)_3$, or $C(=O)NH(CH_2)_{1-3}C(=O)OH$;

R^5 is H;

R^4 and R^5 in combination form an optionally substituted heterocycle;

R^6 is selected from H;

R^7 is selected from, optionally substituted carbocycle, optionally substituted heterocycle, or $-(CH_2)_{1-3}$-optionally substituted carbocycle.

A further embodiment is a compound of formula (II):

wherein:

Q is S;

W is N;

X is C or N, provided that when Y and Z are C, X is N;

Y is C or N, provided that when X and Z are C, Y is N;

Z is C or N, provided that when X and Y are C, Z is N;

R^2 is selected from H, optionally substituted carbocycle;

R^3 is optionally substituted C_{1-6}alkyl;

R^4 is selected from, $-C(=O)OCH_3$, -C(=O)-optionally substituted heterocycle, $-C(=O)NH(CH_2)_{0-3}$-optionally substituted heterocycle, $-C(=O)NH(CH_2)_{1-3}SCH_3$, optionally substituted heterocycle, cyano, $-C(=O)NH_2$, -C(=O)NH-optionally substituted C_{1-6}alkyl, $-C(=O)NH(CH_2)_{0-3}$-optionally substituted carbocycle, $-C(=O)NH(CH_2)_{1-3}N(CH_3)_2$, $C(=O)NH(CH_2)_{1-3}C(OCH_3)_2$, $C(=O)NH(CH_2)_{1-3}NHC(=O)OC(CH_3)_3$, $-C(=O)NH(CH_2)_{1-}$

$_3O(CH_2)_{1-3}OH$, $-C(=O)NH(CH_2)_{1-3}C(=O)OCH_3$, $-C(=O)NH(CH_2)_{1-3}OC(CH_3)_3$, or $C(=O)NH(CH_2)_{1-3}C(=O)OH$;

R^5 is H;

R^6 is selected from H;

R^7 is selected from, optionally substituted carbocycle, optionally substituted heterocycle, or $-(CH_2)_{1-3}$-optionally substituted carbocycle.

A further embodiment is a compound of formula (II):

wherein:

Q is S;

W is N;

X is C or N, provided that when Y and Z are C, X is N;

Y is C or N, provided that when X and Z are C, Y is N;

Z is C or N, provided that when X and Y are C, Z is N;

R^2 is an optionally substituted carbocycle;

R^3 is optionally substituted C_{1-6}alkyl;

R^4 is selected from, $-C(=O)OCH_3$, -C(=O)-optionally substituted heterocycle, $-C(=O)NH(CH_2)_{0-3}$-optionally substituted heterocycle, $-C(=O)NH(CH_2)_{1-3}SCH_3$, optionally substituted heterocycle, cyano, $-C(=O)NH_2$, -C(=O)NH-optionally substituted C_{1-6}alkyl, $-C(=O)NH(CH_2)_{0-3}$-optionally substituted carbocycle, $-C(=O)NH(CH_2)_{1-3}N(CH_3)_2$, $C(=O)NH(CH_2)_{1-3}C(OCH_3)_2$, $C(=O)NH(CH_2)_{1-3}NHC(=O)OC(CH_3)_3$, $-C(=O)NH(CH_2)_{1-3}O(CH_2)_{1-3}OH$, -, $-C(=O)NH(CH_2)_{1-3}C(=O)OCH_3$, $-C(=O)NH(CH_2)_{1-3}OC(CH_3)_3$, or $C(=O)NH(CH_2)_{1-3}C(=O)OH$;

R^5 is H;

R^6 is selected from H;

R^7 is optionally substituted carbocycle,.

A further embodiment is a compound of formula (II):

wherein:

Q is S;

W is N;

X is C or N, provided that when Y and Z are C, X is N;

Y is C or N, provided that when X and Z are C, Y is N;

Z is C or N, provided that when X and Y are C, Z is N;

R^2 is an optionally substituted carbocycle;

R^3 is optionally substituted C_{1-6}alkyl;

R^4 is selected from, $-C(=O)OCH_3$, -C(=O)-optionally substituted heterocycle, $-C(=O)NH(CH_2)_{0-3}$-optionally substituted heterocycle, $-C(=O)NH(CH_2)_{1-3}SCH_3$, optionally substituted heterocycle, $-C(=O)NH_2$, $-C(=O)NH(CH_2)_{0-3}$-optionally substituted carbocycle;

R^5 is H;

R^6 is selected from H;

R^7 is optionally substituted carbocycle.

A further embodiment is a compound of formula (II):

wherein:

Q is S;

W is N;

X is C or N, provided that when Y and Z are C, X is N;

Y is C or N, provided that when X and Z are C, Y is N;

Z is C or N, provided that when X and Y are C, Z is N;

R^2 is optionally substituted carbocycle;

R^3 is optionally substituted C_{1-6}alkyl;

R^4 is selected from, $-C(=O)OCH_3$, -C(=O)-optionally substituted heterocycle, $-C(=O)NH(CH_2)_{0-3}$-optionally substituted heterocycle, or $-C(=O)NH(CH_2)_{1-3}SCH_3$;

R^5 is selected from H;

R^6 is selected from H;

R^7 is optionally substituted carbocycle.

A further embodiment is a compound of formula (II) selected from:

Methyl N-{4-(4-methoxyphenoxy)-6-[(thien-2-ylmethyl)amino]-1,3,5-triazin-2-yl}-L-leucinate;

Methyl N-[4-(4-methoxyphenoxy)-6-(2-pyridin-4-ylethyl)-1,3,5-triazin-2-yl]-L-leucinate;

Methyl N-[4-[(2,3-dihydroxypropyl)amino]-6-(4-methoxyphenoxy)-1,3,5-triazin-2-yl]-L-leucinate;

Methyl N-{4-(4-methoxyphenoxy)-6-[(tetrahydrofuran-2-ylmethyl)amino]-1,3,5-triazin-2-yl}-L-leucinate;

Methyl N-[4-[(3-fluorobenzyl)amino]-6-(4-methoxyphenoxy)-1,3,5-triazin-2-yl]-L-leucinate;
Methyl N-[4-[(2-methoxybenzyl)amino]-6-(4-methoxyphenoxy)-1,3,5-triazin-2-yl]-L-leucinate;
Methyl N-[4-[(3,5-difluorobenzyl)amino]-6-(4-methoxyphenoxy)-1,3,5-triazin-2-yl]-L-leucinate;
Methyl N-[4-[(3,5-dichlorobenzyl)amino]-6-(4-methoxyphenoxy)-1,3,5-triazin-2-yl]-L-leucinate;
Methyl N-[4-(benzylamino)-6-(4-methoxyphenoxy)-1,3,5-triazin-2-yl]-L-leucinate;
Methyl N-[4-(butylamino)-6-(4-methoxyphenoxy)-1,3,5-triazin-2-yl]-L-leucinate;
Methyl N-[4-(pentylamino)-6-(4-methoxyphenoxy)-1,3,5-triazin-2-yl]-L-leucinate;
Methyl N-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}glycinate;
(2R)-2-({4-[(5-Chloro-2-methylphenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}amino)-4-methylpentan-1-ol;
Methyl N-{4-[(5-chloro-2-methylphenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-leucinate;
Methyl N-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-leucinate;
1-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}pyrrolidin-3-ol;
N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-leucinamide;
N^2-(3-fluorophenyl)-N^4-isopentyl-6-[(4-methoxyphenyl)thio]-1,3,5-triazine-2,4-diamine
(2S)-2-({4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}amino)-4-methylpentan-1-ol;
Methyl N-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-phenylalaninate;
2-({4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}amino)propan-1-ol;
N^2-(2,2-Dimethoxyethyl)-N^4-(3-fluorophenyl)-6-[(4-methoxyphenyl)thio]-1,3,5-triazine-2,4-diamine;
Ethyl N-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-b-alaninate;
3-[{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}(methyl)amino]propanenitrile;

Methyl N-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-alaninate;

Methyl N-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-D-leucinate;

Methyl N-{4-[(2,3-dihydroxypropyl)thio]-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-L-leucinate;

Methyl N-{4-[(3-fluorophenyl)amino]-6-[(3-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-leucinate;

Methyl N-{4-[(3-fluorophenyl)(methyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-leucinate;

(2R)-2-({4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}amino)-4-methylpentan-1-ol;

Methyl N-{4-[(3-fluorophenyl)amino]-6-[(2-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-leucinate;

Methyl N-[4-[(3-fluorophenyl)amino]-6-(phenylthio)-1,3,5-triazin-2-yl]-L-leucinate;

Methyl N-[4-[(3-fluorophenyl)amino]-6-(quinolin-2-ylthio)-1,3,5-triazin-2-yl]-L-leucinate;

Methyl N-{4-[(4-aminophenyl)thio]-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-L-leucinate;

Methyl N-{4-[(3-bromophenyl)thio]-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-L-leucinate;

Methyl N-[4-[(3-fluorophenyl)amino]-6-(pyrimidin-2-ylthio)-1,3,5-triazin-2-yl]-L-leucinate;

Methyl N-{4-{[2-(dimethylamino)ethyl]thio}-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-L-leucinate;

Methyl N-{4-({1-[2-(dimethylamino)ethyl]-1H-tetrazol-5-yl}thio)-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-L-leucinate;

Methyl N-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)sulfinyl]-1,3,5-triazin-2-yl}-L-leucinate;

Methyl N-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)sulfonyl]-1,3,5-triazin-2-yl}-L-leucinate;

N^1-[2-(Dimethylamino)ethyl]-N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-leucinamide;

N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-N^1-(tetrahydrofuran-2-ylmethyl)-L-leucinamide;

N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-N^1-(2-morpholin-4-ylethyl)-L-leucinamide;

N^1-{2-[(tert-Butoxycarbonyl)amino]ethyl}-N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-leucinamide;

N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-N^1-(pyridin-3-ylmethyl)-L-leucinamide;

N^1-(3,5-Difluorobenzyl)-N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-leucinamide;

N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-N^1-(2-furylmethyl)-L-leucinamide;

N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-N^1-[3-(2-oxopyrrolidin-1-yl)propyl]-L-leucinamide;

N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-N^1-(3-methoxybenzyl)-L-leucinamide;

N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-N^1-(2-piperidin-1-ylethyl)-L-leucinamide;

N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-N^1-[2-(2-hydroxyethoxy)ethyl]-L-leucinamide;

N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-N^1-phenyl-L-leucinamide;

N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-N^1-propyl-L-leucinamide;

N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-N^1-(2-pyrrolidin-1-ylethyl)-L-leucinamide;

N^2-(3-fluorophenyl)-6-[(4-methoxyphenyl)thio]-N^4-[(1S)-3-methyl-1-(morpholin-4-ylcarbonyl)butyl]-1,3,5-triazine-2,4-diamine;

N^1-{2-[4-(aminosulfonyl)phenyl]ethyl}-N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-leucinamide;

N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-N^1-[2-(1-methylpyrrolidin-2-yl)ethyl]-L-leucinamide;

N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-N^1-(3-methoxypropyl)-L-leucinamide;

N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-N^1-(pyridin-2-ylmethyl)-L-leucinamide;

Methyl N-{2-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-4-yl}-L-leucinate;

Methyl N-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-L-leucinate;

N-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-leucine;

N-{4-[(3-fluorophenyl)(methyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-L-leucine;

N-{4-chloro-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N-methyl-leucine;

Methyl N-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N-methylleucinate;

N^2-[4-[(3-fluorophenyl)amino]-6-(quinolin-2-ylthio)pyrimidin-2-yl]-N^1-(tetrahydrofuran-2-ylmethyl)-L-leucinamide;

N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-(2-furylmethyl)-L-leucinamide;

N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-(tetrahydrofuran-2-ylmethyl)-L-leucinamide;

N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-propyl-L-leucinamide;

N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-(2-morpholin-4-ylethyl)-L-leucinamide;

N^1-(2,2-methoxyethyl)-N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-L-leucinamide;

N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-(2-pyridin-2-ylethyl)-L-leucinamide;

Methyl N-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-L-leucylglycinate;

N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-[3-(1H-imidazol-1-yl)propyl]-L-leucinamide;

N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-(2-isopropoxyethyl)-L-leucinamide;

N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-[2-(methylthio)ethyl]-L-leucinamide;

N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-pentyl-L-leucinamide;

N-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-L-leucylglycine;

N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-[2-(1H-imidazol-5-yl)ethyl]-L-leucinamide;

N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-methoxy-N^1-methyl-L-leucinamide;

N^2-{2-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-4-yl}-N^1-(2-morpholin-4-ylethyl)-L-leucinamide;

N^2-{2-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-4-yl}-N^1-(tetrahydrofuran-2-ylmethyl)-L-leucinamide;

N^2-{2-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-4-yl}-N^1-propyl-L-leucinamide;

(S)-2-[4-(3-Cyano-phenylamino)-6-(thiazol-2-ylsulfanyl)-pyrimidin-2-ylmethyl]-4-methyl-pentanoic acid (tetrahydro-furan-2-ylmethyl)-amide;

(S)-2-[4-(3-Cyano-phenylamino)-6-(pyridin-2-ylsulfanyl)-pyrimidin-2-ylmethyl]-4-methyl-pentanoic acid (tetrahydro-furan-2-ylmethyl)-amide;

N^2-{4-[((3-Methyl-propyl)thio)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-*N*^{1}-(tetrahydrofuran-2-ylmethyl)-L-leucinamide;

N^2-{4-[(2-Pyridyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-*N*^{1}-(tetrahydrofuran-2-ylmethyl)-L-leucinamide;

(S)-2-[4-(3-Cyano-phenylamino)-6-(4-methoxy-phenylsulfanyl)-pyrimidin-2-ylmethyl]-4-methyl-pentanoic acid (2-methylsulfanyl-ethyl)-amide;

N^2-{2-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-4-yl}-*N*^{1}-1-morpholin-4-yl-L-leucinamide;

2-[6-(3-Fluoro-phenylamino)-2-(4-methoxy-phenylsulfanyl)-pyrimidin-4-ylamino]-4-methyl-pentanoic acid methyl ester;

(S)-2-[6-(3-Fluoro-phenylamino)-4-(4-methoxy-phenylsulfanyl)-pyridin-2-ylamino]-4-methyl-pentanoic acid methyl ester;

N^2-(3-Fluoro-phenyl)-6-(4-methoxy-phenylsulfanyl)-N^4-(3-methyl-1-pyridin-2-yl-butyl)-pyrimidine-2,4-diamine;

N^4-(3-Fluoro-phenyl)-6-(4-methoxy-phenylsulfanyl)-N^2-(3-methyl-1-pyridin-2-yl-butyl)-pyrimidine-2,4-diamine;

(S)-2-[4-(3-Cyano-phenylamino)-6-(quinolin-8-ylsulfanyl)-pyrimidin-2-ylmethyl]-4-methyl-pentanoic acid (tetrahydro-furan-2-ylmethyl)-amide;
(S)-2-[4-(4-Amino-phenylsulfanyl)-6-(3-cyano-phenylamino)-pyrimidin-2-ylmethyl]-4-methyl-pentanoic acid (tetrahydro-furan-2-ylmethyl)-amide;
(S)-2-[3-(3-Fluoro-phenylamino)-5-(4-methoxy-phenylsulfanyl)-phenylamino]-4-methyl-pentanoic acid methyl ester;
(S)-2-[2-(3-Fluoro-phenylamino)-6-(4-methoxy-phenylsulfanyl)-pyridin-4-ylamino]-4-methyl-pentanoic acid methyl ester;
(S)-2-[6-(3-Fluoro-phenylamino)-4-(4-methoxy-phenylsulfanyl)-1-oxy-pyridin-2-ylamino]-4-methyl-pentanoic acid methyl ester;
(S)-2-[4-(3-Fluoro-phenylamino)-6-(4-methoxy-phenylsulfanyl)-pyridin-2-ylamino]-4-methyl-pentanoic acid methyl ester;

A further embodiment is a compound according to formula (I) and/or formula (II), for use as a medicament.

A further embodiment is the use of a compound according to formula (I) and/or formula (II), in the manufacture of a medicament for the treatment or prophylaxis of disorders associated with β-amyloid production.

A further embodiment is the use of a compound according to formula (I) and/or formula (II), in the manufacture of a medicament for the treatment or prophylaxis of Alzheimer's disease or Down's syndrome.

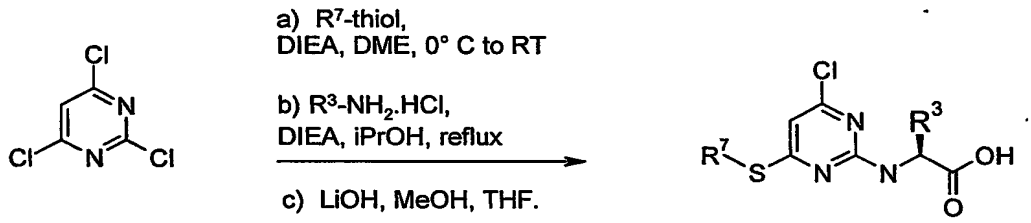
A further embodiment is a method for the treatment of neurological disorders associated with β-amyloid production comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound according to formula (I) and/or formula (II).

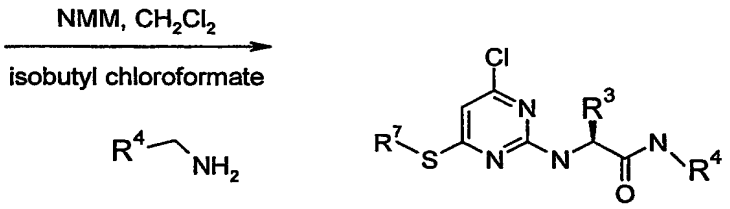
A further embodiment is a method for inhibiting γ-secretase activity comprising administering to a warm-blooded animal in need of such inhibition a therapeutically effective amount of a compound according to formula (I) and/or formula (II).

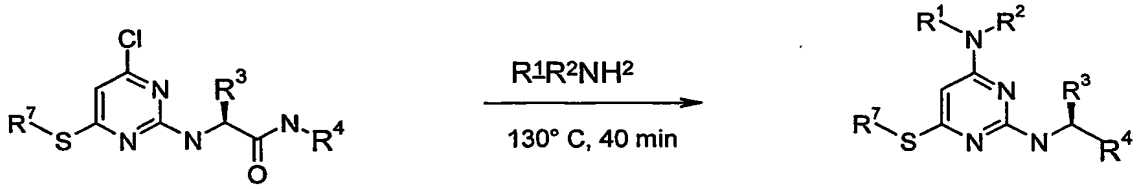
A further embodiment is a method for the treatment or prophylaxis of Alzheimer's disease or Down's syndrome comprising administring to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound according to formula (I) and/or formula (II).

A further embodiment is a pharmaceutical composition comprising a compound according to formula (I) and/or formula (II), or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, together with at least one pharmaceutically acceptable carrier, diluent or excipient.

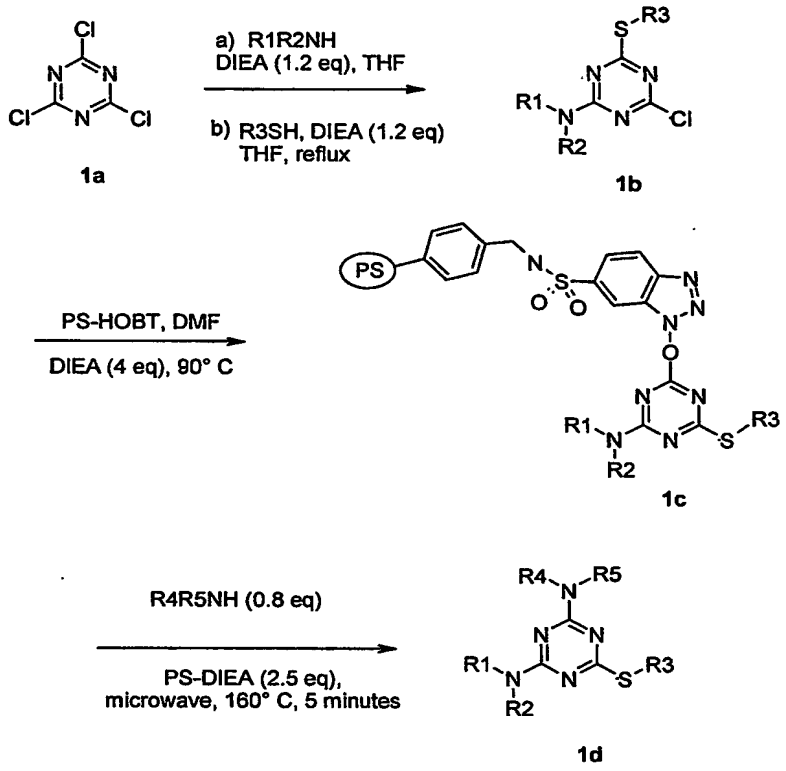
A further embodiment is a process for preparing a compound of formula (I), which process comprises:







A further embodiment is a process for preparing a compound of formula (II) which process comprises:


a) R1R2NH
DIEA (1.2 eq), THF
b) R3SH, DIEA (1.2 eq)
THF, reflux
1a
1b
PS-HOBT, DMF
DIEA (4 eq), 90° C
PS
1c
R4R5NH (0.8 eq)
PS-DIEA (2.5 eq),
microwave, 160° C, 5 minutes
1d
a) R4R5NH
DIEA (2.2 eq), THF
Relfux 4 h
1b
1d

Definitions

Unless specified otherwise within this application, the nomenclature used in this application generally follows the examples and rules stated in *Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F, and H*, Pergamon Press, Oxford, 1979, which is incorporated by references herein for its exemplary chemical structure names and rules on naming chemical structures. Optionally, a name of a compound may be generated using a chemical naming program: ACD/ChemSketch, Version 5.09/September 2001, Advanced Chemistry Development, Inc., Toronto, Canada.

As used in this application, the term "optionally substituted," as used herein, means that substitution is optional and therefore it is possible for the designated atom to be unsubstituted. In the event a substitution is desired then such substitution means that any number of hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the normal valency of the designated atom is not exceeded, and that the substitution results in a stable compound. For example when a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. If no selection is provided then the substituent shall be selected from :

aniline, anisole, benzene sulfonamide, cyano, carbocycle, heterocycle, halogen, hydroxy, NH_2, NO_2, C_{1-6}alkyl, C_{1-6}alkoxy, $-C(=O)NH_2$, $C(=O)OCH_2CH_3$, $-N(CH_3)_2$, $-(CH_2)_{1-3}N(CH_3)_2$, $O(CH_2)_{1-3}OH$, SCH_3, NO_2, CF_3, alkenyl, alkynyl.

When any variable (e.g., R^1, R^7, R^a, R^e etc.) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-3 R^1, then said group may optionally be substituted with 0,1, 2 or 3 R^1 groups and R^e at each occurrence is selected independently from the definition of R^e. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. In addition the range "according to claims 1-9" means claims 1, 2, 3, 4, 5, 6, 7, 8, or 9.

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or

racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. When required, separation of the racemic material can be achieved by methods known in the art. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, "C_{1-6} alkyl" denotes alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, pentyl, and hexyl. As used herein, "C_{1-3} alkyl", whether a terminal substituent or an alkylene group linking two substituents, is understood to specifically include both branched and straight-chain methyl, ethyl, and propyl.

As used herein, "alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either a straight or branched configuration with one or more unsaturated carbon-carbon bonds that may occur at any stable point along the chain. Examples of "C_{3-6}alkenyl" include, but are not limited to, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, 2-pentenyl, 3-pentenyl, hexenyl, and the like.

As used herein, "alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either a straight or branched configuration with one or more carbon-carbon triple bonds that may

occur at any stable point along the chain, such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, and the like.

As used herein, "alkoxy" or "alkyloxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and s-pentoxy. Preferred alkoxy groups are methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy. Similarly, "alkylthio" or "thioalkoxy" represent an alkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge.

As used herein, "carbocycle" is intended to mean any stable 3- to 7-membered monocyclic or bicyclic or 7- to 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, bicyclooctane, bicyclononane, bicyclodecane (decalin), bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin).

As used herein, "halo" or "halogen" refers to fluoro, chloro, bromo, and iodo. "Counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate, and the like. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where v=1 to 3 and w=1 to (2v+1)). Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, pentachloroethyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, heptafluoropropyl, and heptachloropropyl. "Haloalkoxy" is intended to mean a haloalkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge; for example trifluoromethoxy, pentafluoroethoxy, 2,2,2-trifluoroethoxy, and the like. "Halothioalkoxy" is intended to mean a haloalkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge.

As used herein, the term "heterocycle" or "heterocyclic" refersto a ring-containing monovalent and divalent radicals having one or more heteroatoms, independently selected

from N, O and S, as part of the ring structure and comprising at least 3 and up to about 20 atoms in the rings. Heterocyclic groups may be saturated or unsaturated, containg one or more double bonds, and heterocyclic groups may contain more that one ring. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. If specifically noted, nitrogen in the heterocycle may optionally be quaternized. It is understood that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another.

Examples of heterocycles include, but are not limited to, 1H-indazole, 2-pyrrolidonyl, 2H, 6H-1, 5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidonyl, 4aH-carbazole, 4H-quinolizinyl, 6H-1, 2,5-thiadiazinyl, acridinyl, azetidine, aziridine, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, carbazolyl, 4aH-carbazolyl, b-carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dioxolane, furyl, 2,3-dihydrofuran, 2,5-dihydrofuran, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, homopiperidinyl, imidazolidine, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxirane, oxazolidinylperimidinyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, piperidonyl, 4-piperidonyl, purinyl, pyranyl, pyrrolidine, pyrroline, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, N-oxide-pyridinyl, pyridyl, pyrimidinyl, pyrrolidinone, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, carbolinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrazolyl, thiophane, thiophene. thiotetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, thiirane, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, xanthenyl.

As used herein, "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Prodrugs" are intended to include any covalently bonded carriers that release the active parent drug according to formula (I) in vivo when such prodrug is administered to a mammalian subject. Prodrugs of a compound of formula (I) are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved,

either in routine manipulation or in vivo, to the parent compound. Prodrugs include compounds of formula (I) wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug or compound of formula (I) is administered to a mammalian subject, cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formula (I), and the like.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The compounds described herein may be provided or delivered in a form suitable for oral use, for example in a tablet, lozenge, hard and soft capsule, aqueous solution, oily solution, emulsion, and suspension. The compounds may also be provided for topical administration, for example, as a cream, ointment, gel, spray, or aqueous solutions, oily solutions, emulsions or suspensions. The compounds described herein may also be provided in a form suitable for nasal administration for example, as a nasal spray, nasal drops, or dry powder. The compositions may also be administered to the vagina or rectum in the form of a suppository. The compounds described herein may also be administered parentally, for example by intravenous, intravesicular, subcutaneous, intrathoracially, intracerebroventricularly, or intramuscular injection or infusion. The compounds may be administered by insufflation (for example as a finely divided powder). The compounds may also be administered transdermally, sublingually, .

The compositions of the invention may accordingly be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more coloring, sweetening, flavoring and/or preservative agents.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. The size of the dose for therapeutic or prophylactic purposes of a compound described herein will naturally vary according to the nature and severity of the

conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

An effective amount of a compound described herein for use in therapy of Alzheimer's Disease is an amount sufficient to symptomatically relieve in a warm-blooded animal, particularly a human the cognitive symptoms, to slow the progression of worsening cognitive symptoms, or to reduce in patients with cognitive symptoms the risk of getting worse (progressing to dementia or worsening the present degree of dementia).

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid that is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

Salts include, but are not limited to, pharmaceutically acceptable salts. Examples of pharmaceutically acceptable salts of compounds of the present invention include but are not limited to the following: acetate, bicarbonate, bisulfate, bisulfite, carbonate, hydrobromide, hydrochloride, phosphate/diphosphate, sulfate, choline, diethanolamine, ethylenediamine, meglumine, aluminum, calcium, magnesium, nitrate, potassium, pyrosulfate, and sodium.

The term composition is intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included. Tablets, powders, cachets, and capsules can be used, as solid dosage forms suitable for oral administration.

Liquid form compositions include solutions, suspensions, and emulsions. Sterile water or water-propylene glycol solutions of the active compounds may be mentioned as an example of liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution. Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous

suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

The pharmaceutical compositions can be in unit dosage form. In such form, the composition is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparations, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

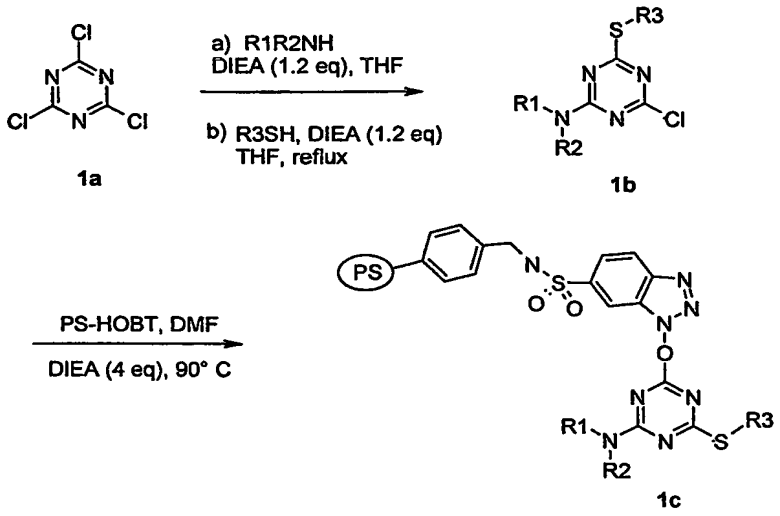
Synthesis

The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Such methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety by reference.

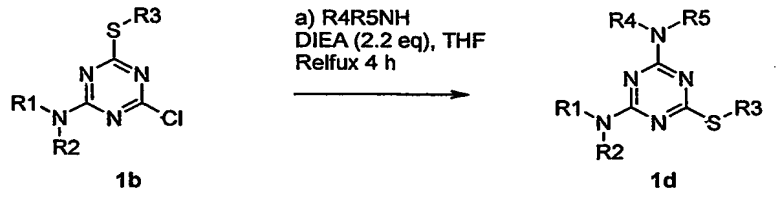
The novel compounds of this invention may be prepared using the reactions and techniques described in this application. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents, which are compatible with the reaction conditions, will be readily apparent to one skilled in the art and alternate methods must then be used.

An example of such a process is illustrated herein.

Method C-1



Method C-2



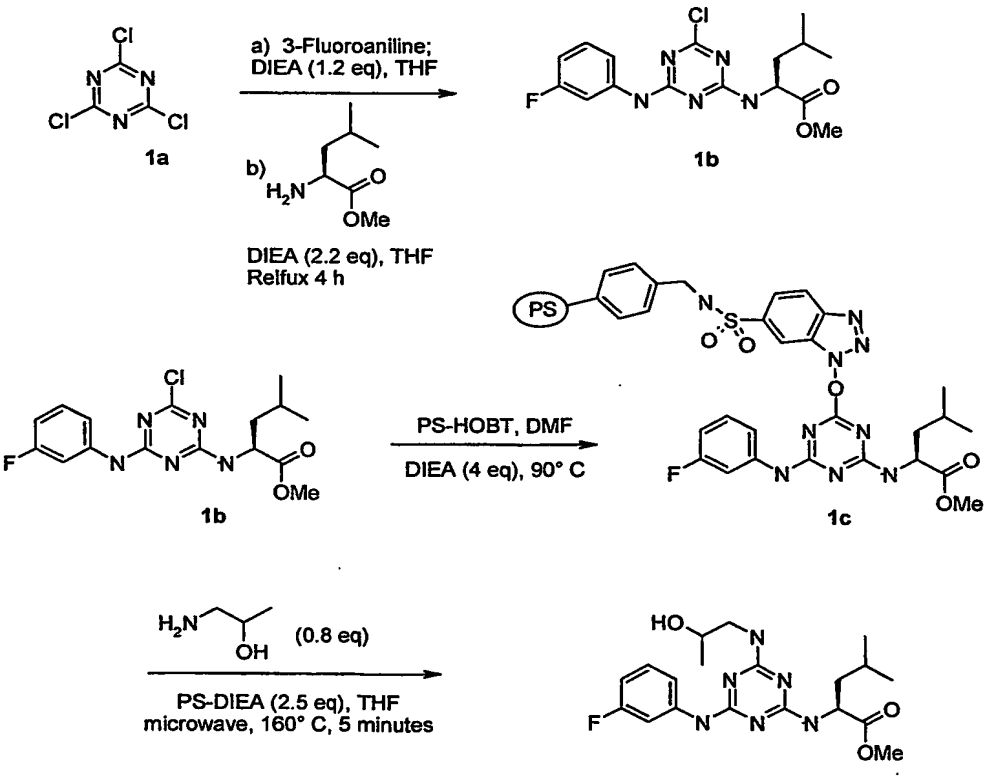
Examples

Chemical abbreviations used in the Examples are defined as follows: "BOC" denotes N-tert-butoxycarbonyl, "CBZ" denotes carbobenzyloxy; "DBU" denotes 1,8-diazabicyclo [5.4.0] undec-7-ene; "DCM" denotes dichloromethane; "DMAP" denotes 4-dimethylaminopyridine trifluoroacetic acid; "DMF" denotes N, N-dimethylformamide; DME denotes ethylene glycol dimethyl ether; DIEA denotes diisopropylethylamine; KOtBu denotes potassium tert-butoxide; Et2O denotes diethyl ether, MeOH deontes methyl alchol, iPrOH deontes isopropyl alcohol; "EDAC-HCl" or EDCI denotes 1-Ethyl-3-(dimethylaminopropyl)carbodiimide

hydrochloride; "HOBt" denotes hydroxybenzotriazole; "NMM" denotes N-methylmorpholine; "p-TSA" denotes p-toluenesulfonic acid "TBAB" denotes tetrabutylammonium bromide; "TEA" denotes triethylamine; "TFA" denotes triflouroacetic acid; "THF" denotes tetrahydrofuran, "PS" denotes polystyrene, Tos-Cl denotes p-toluenesulfonyl chloride, "min." denotes minutes; "h" denotes hours; "RT" denotes room temperature. Unless otherwise noted, organic solutions were "dried" over anhydrous sodium sulfate.

LC/MS HPLC method: Agilent Zorbax 5µ SB-C8 column 2.1mm x 5 cm. Solvents: A = H_2O with 0.05% TFA, B =10% H_2O, 90% Acetonitrile, 0.05% TFA. Gradient: (10-90%B over 3 min., 90% B hold thru 4 min., -10% B at 5 min. and hold at 10% B until 6 min).

Example 1. Methyl *N*-{4-[(3-fluorophenyl)amino]-6-[(2-hydroxypropyl)amino]-1,3,5-triazin-2-yl}-L-leucinate (1)

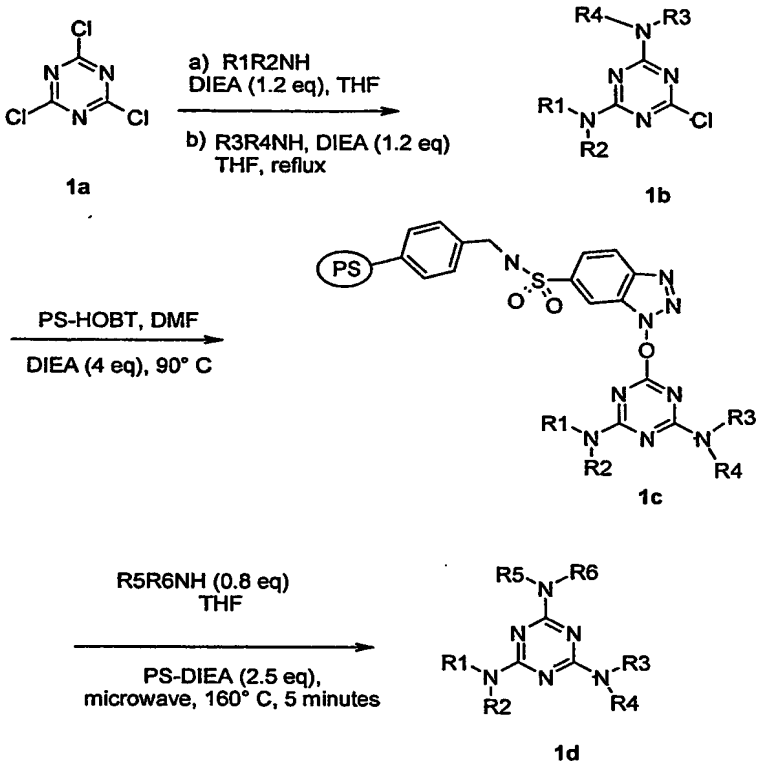


To a stirred solution of cyanuric chloride (**1a**) (2.23 g, 12.1 mmol) in THF (50 mL) was added 3-fluoroaniline (1.17 mL, 12.1 mmol) and DIEA (8.4 mL, 48.4 mmol). The mixture was stirred for 1 hour, leucine methyl ester hydrochloride (2.23 g, 21.1 mmol) was added and the solution heated to reflux for 4 h. The mixture was cooled to room temperature and the solvent removed *in vacuo*. The residual oil was partitioned between CH_2Cl_2 and 1N HCl (100 mL). The organic layer was separated, washed with NaCl (sat.) and dried over Na_2SO_4. The volatiles were removed to give **1b** as a crude foam (3.38 g, 76%). A portion of the resultant material (2.16 g, 4.7 mmol) was dissolved in DMF (30 mL) and to this was added PS-HOBT (3.38 g, 4.7 mmol), followed by DIEA (1.05 mL, 5.8 mmol). The suspension was slowly stirred at 90° C for 2h. The resin was filtered and washed with CH_2Cl_2 (3 x 100 mL), then Et_2O (1 x 100 mL) and dried *in vacuo* to give a yellow, free-flowing resin **1c** (4.84 g). A portion of the resultant resin (0.200 g) was added to PS-DIEA (0.200 g, 4 mmol/g) in THF (1.5 mL). To this suspension was added 2-hydroxyaminopropane and the mixture was heated to 160 °C for five minutes in a Personal Chemistry Smithsynthesizer microwave reactor. The reaction was filtered, washed with CH_2Cl_2, and the solvent was removed *in vacuo* to give the title compound **1** as a white foam (0.041 g). ^{1}H NMR (300 MHz, DMSO-*d6*) δ 0.88-0.92 (m, 6H), 1.05-1.07 (m, 3H), 1.48-1.52 (m, 1H), 1.72-1.75 (m, 2H), 3.22-3.27 (m, 1H), 3.59-3.61 (m, 3H), 3.77-3.81 (m, 1H), 4.44-4.78 (m, 2H), 7.18-7.25 (m, 2H), 7.39-7.44 (m, 1H), 7.82-7.95 (m, 1H), 9.01-9.11 (m, 1H), MS APCI, *m/z* = 407(M+1). LC/MS t_R = 2.11 min.

By analogy, Examples 2-26 (Table 1) were prepared according to general method A.

Table 1. Method A, General Procedure for Examples 1-26

Method A



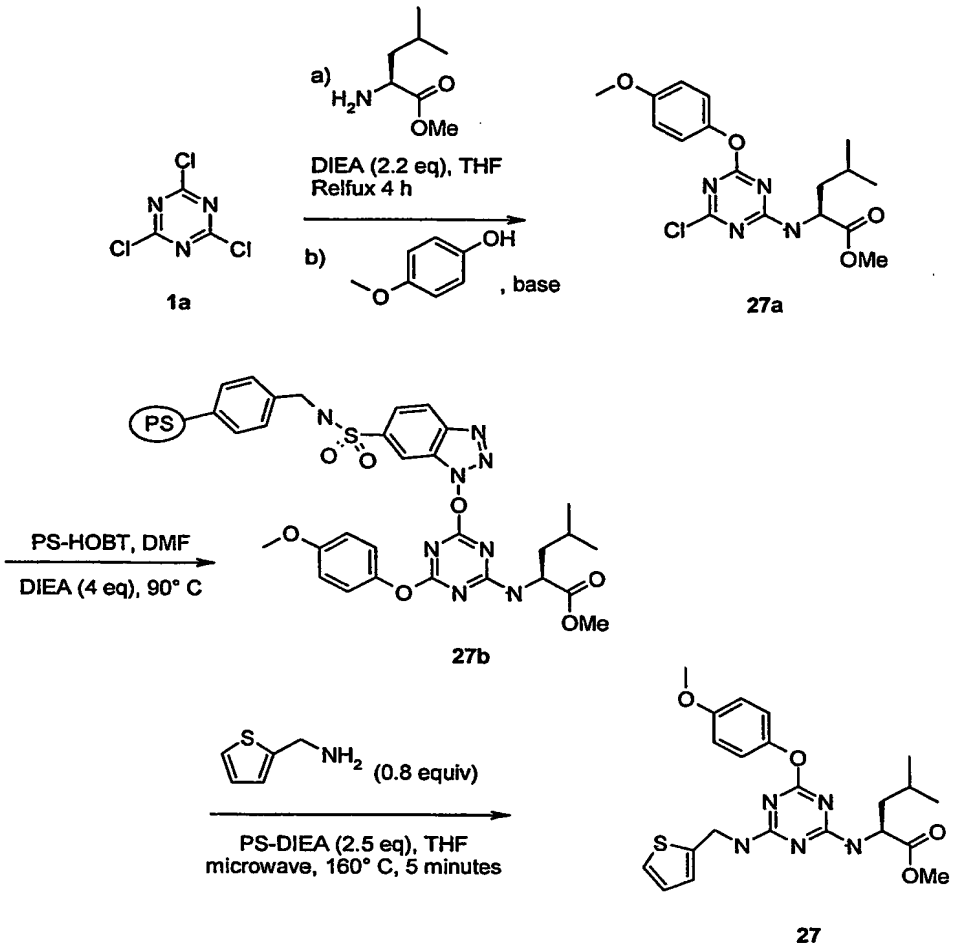
Example	Name	LC/MS t_R (min)	MS APCI, *m/z* (M+1)
1	Methyl *N*-{4-[(3-fluorophenyl)amino]-6-[(2-hydroxypropyl)amino]-1,3,5-triazin-2-yl}-L-leucinate	2.11	407
2	Methyl *N*-{4-[(3-fluorophenyl)amino]-6-morpholin-4-yl-1,3,5-triazin-2-yl}-L-leucinate	2.35	419
3	(2*R*)-2-({4-[(3-Fluorophenyl)amino]-6-[(3-methoxypropyl)amino]-1,3,5-triazin-2-yl}amino)-4-methylpentan-1-ol	2.13	393

4	Methyl *N*-{4-[(3-fluorophenyl)amino]-6-[(4-methoxybenzyl)amino]-1,3,5-triazin-2-yl}-D-leucinate	2.63	469
5	Methyl *N*-{4-[(cyclopropylmethyl)amino]-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-D-leucinate	2.53	403
6	Methyl *N*-{4-[(3-fluorophenyl)amino]-6-[(3-methoxypropyl)amino]-1,3,5-triazin-2-yl}-D-leucinate	2.35	421
7	(2*R*)-2-({4-[(Cyclopropylmethyl)amino]-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}amino)-4-methylpentan-1-ol	2.29	375
8	Methyl *N*-{4-[(3-fluorophenyl)amino]-6-[(tetrahydrofuran-2-ylmethyl)amino]-1,3,5-triazin-2-yl}-L-leucinate	2.42	433
9	Methyl *N*-(4-[(3-fluorophenyl)amino]-6-{[3-(1*H*-imidazol-1-yl)propyl]amino}-1,3,5-triazin-2-yl)-L-leucinate	1.93	457
10	Methyl *N*-{4-[(2-anilinoethyl)amino]-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-L-leucinate	2.43	468
11	Methyl *N*-{4-[(3-fluorophenyl)amino]-6-[(2-hydroxy-2-phenylethyl)amino]-1,3,5-triazin-2-yl}-L-leucinate	2.42	469
12	Methyl *N*-(4-[(3-fluorophenyl)amino]-6-{[2-(4-methoxyphenyl)ethyl]amino}-1,3,5-triazin-2-yl)-L-leucinate	2.63	483

13	Methyl *N*-{4-[(2,3-dihydroxypropyl)amino]-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-L-leucinate	1.95	423
14	Methyl *N*-[4-[(3-fluorophenyl)amino]-6-(3-hydroxypyrrolidin-1-yl)-1,3,5-triazin-2-yl]-L-leucinate	2.12	419
15	Methyl *N*-{4-[(2-amino-2-oxoethyl)(methyl)amino]-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-L-leucinate	1.98	420
16	(2*R*)-2-[(4-[(3-Fluorophenyl)amino]-6-{[2-(4-methoxyphenyl)ethyl]amino}-1,3,5-triazin-2-yl)amino]-4-methylpentan-1-ol	2.36	455
17	Methyl *N*-{4-[(2-cyanoethyl)(methyl)amino]-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-L-leucinate	2.36	416
18	Methyl *N*-[4-[(3-fluorophenyl)amino]-6-(4-pyridin-4-ylpiperazin-1-yl)-1,3,5-triazin-2-yl]-L-leucinate	2.05	495
19	Methyl *N*-{4-(4-cyano-4-phenylpiperidin-1-yl)-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-L-leucinate	2.85	518
20	Methyl *N*-{4-[(3-fluorophenyl)amino]-6-[(3-hydroxy-2,2-dimethylpropyl)amino]-1,3,5-triazin-2-yl}-L-leucinate	2.26	435

21	Methyl *N*-{4-[(3-fluorophenyl)amino]-6-[(3-morpholin-4-ylpropyl)amino]-1,3,5-triazin-2-yl}-L-leucinate	1.80	476
22	Methyl *N*-{4-({2-[4-(aminosulfonyl)phenyl]ethyl}amino)-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-L-leucinate	2.33	532
23	Methyl *N*-{4-{[2-(dimethylamino)ethyl]amino}-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-L-leucinate	1.92	420
24	Methyl *N*-(4-[(3-fluorophenyl)amino]-6-{[2-(2-hydroxyethoxy)ethyl]amino}-1,3,5-triazin-2-yl)-L-leucinate	2.05	437
25	Methyl *N*-{4-[(3-fluorophenyl)amino]-6-[(4-hydroxybutyl)amino]-1,3,5-triazin-2-yl}-L-leucinate	2.13	421
26	Methyl *N*-(4-[(3-fluorophenyl)amino]-6-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}-1,3,5-triazin-2-yl)-L-leucinate	2.21	474

Example 27. Methyl *N*-{4-(4-methoxyphenoxy)-6-[(thien-2-ylmethyl)amino]-1,3,5-triazin-2-yl}-L-leucinate (27).



A portion of methyl *N*-[4-chloro-6-(4-methoxyphenoxy)-1,3,5-triazin-2-yl]-L-leucinate **27a** (0.70 g, 1.8 mmol) was dissolved in DMF (5 mL) and to this was added PS-HOBT (1.00 g, 1.4 mmol), followed by DIEA (0.6 mL). The suspension was carefully stirred at 90° C for 2h. The resin was filtered and washed with CH_2Cl_2 (3 x 100 mL), then Et_2O (1 x 100 mL) and dried *in vacuo* to give a yellow free-flowing resin (1.65 g). A portion of the resultant resin (0.225 g) was added to PS-DIEA (0.200 g, 4 mmol/g) in THF (1.5 mL). To this suspension was added thiophene-2-methylamine (0.014 g, 0.12 mmol) and the mixture was heated to 160° C for five minutes in a Smithsynthesizer microwave reactor vessel. The reaction was filtered, washed with CH_2Cl_2, and the solvent was removed *in vacuo* to give the title compound **27** as a white foam (0.038 g). ^{1}H NMR (300 MHz, DMSO-*d6*) δ 0.82-0.88 (m, 6H), 1.40-1.46 (m, 1H), 1.62-1.66 (m, 2H), 3.57 (s, 3H), 3.74 (s, 3H), 4.49-4.58 (m, 3H),

6.90-6.92 (m, 4H), 7.02-7.08 (m, 2H), 7.33 (m, 1H), 7.74-7.76 (m, 1H). MS APCI, $m/z = 458$ (M+1). LC/MS $t_R = 2.71$ min.

Intermediate **27b** was prepared by analogy to Example **1**, except 4-methoxyphenol was used in the presence of a suitable base, such as potassium carbonate, sodium hydride or potassium tert-butoxide.

By analogy Examples 28-37 (Table 2) were prepared.

Method B

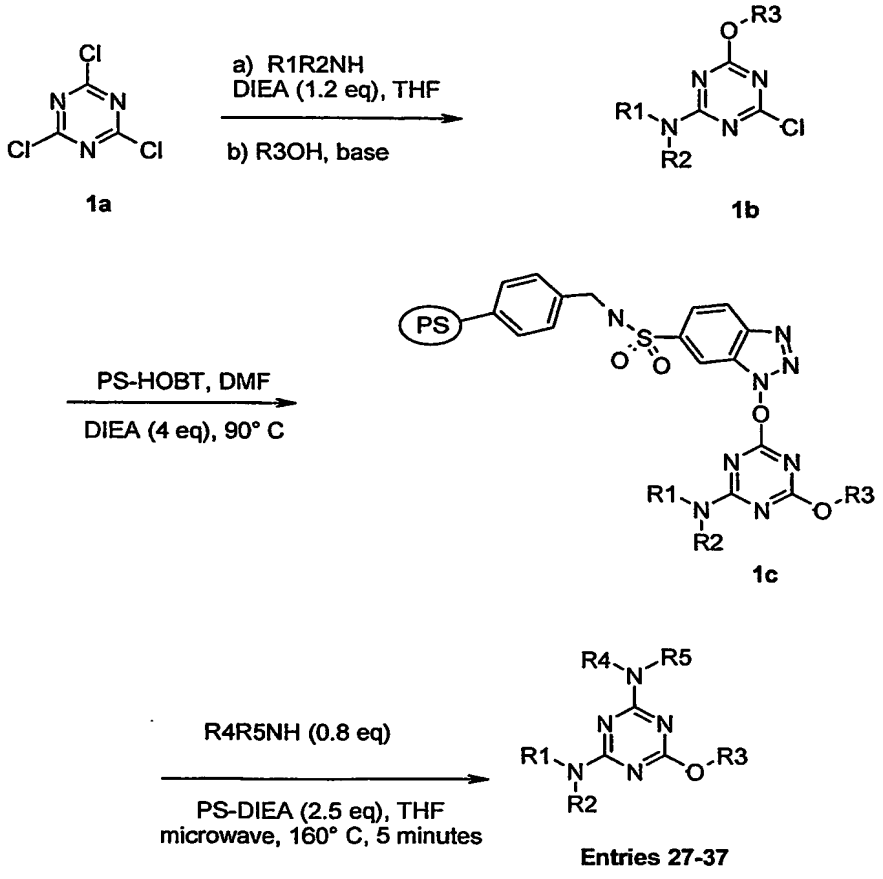
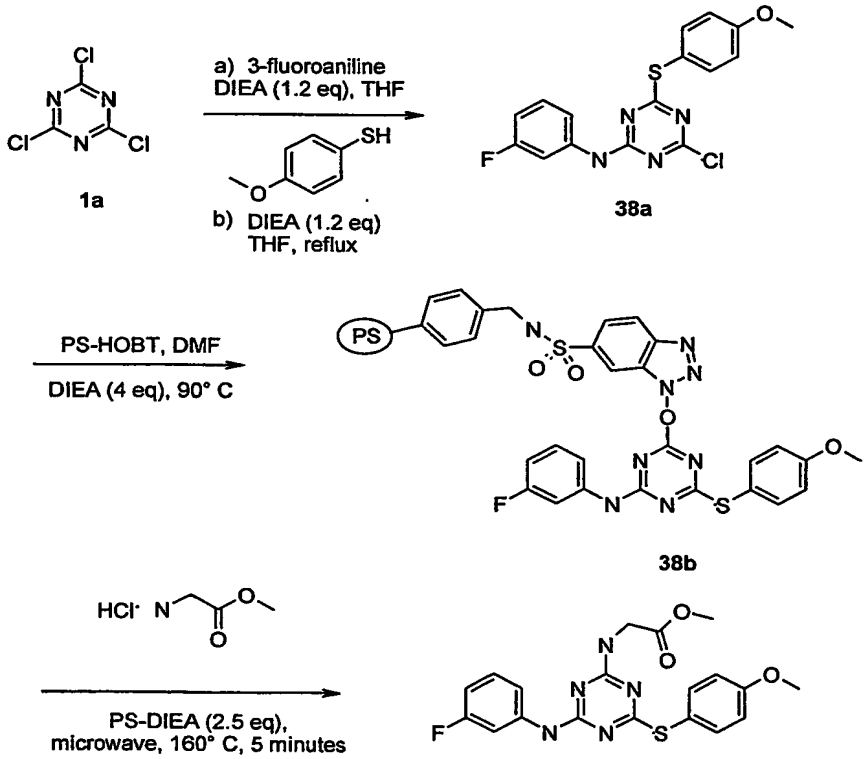


Table 2. Method B, General Procedure for Examples 27-37.

Examples	Name	LC/MS t_R (min)	MS APCI, *m/z* (M+1)
27	Methyl *N*-{4-(4-methoxyphenoxy)-6-[(thien-2-ylmethyl)amino]-1,3,5-triazin-2-yl}-L-leucinate	2.71	458
28	Methyl *N*-[4-(4-methoxyphenoxy)-6-(2-pyridin-4-ylethyl)-1,3,5-triazin-2-yl]-L-leucinate	2.00	487
29	Methyl *N*-[4-[(2,3-dihydroxypropyl)amino]-6-(4-methoxyphenoxy)-1,3,5-triazin-2-yl]-L-leucinate	1.96	436
30	Methyl *N*-{4-(4-methoxyphenoxy)-6-[(tetrahydrofuran-2-ylmethyl)amino]-1,3,5-triazin-2-yl}-L-leucinate	2.44	446
31	Methyl *N*-[4-[(3-fluorobenzyl)amino]-6-(4-methoxyphenoxy)-1,3,5-triazin-2-yl]-L-leucinate	2.78	470
32	Methyl *N*-[4-[(2-methoxybenzyl)amino]-6-(4-methoxyphenoxy)-1,3,5-triazin-2-yl]-L-leucinate	2.73	482
33 2	Methyl *N*-[4-[(3,5-difluorobenzyl)amino]-6-(4-methoxyphenoxy)-1,3,5-triazin-2-yl]-L-leucinate	2.86	488
34	Methyl *N*-[4-[(3,5-dichlorobenzyl)amino]-6-(4-methoxyphenoxy)-1,3,5-triazin-2-yl]-L-leucinate	3.05	520, 522

35	Methyl *N*-[4-(benzylamino)-6-(4-methoxyphenoxy)-1,3,5-triazin-2-yl]-L-leucinate	2.77	452
36	Methyl *N*-[4-(butylamino)-6-(4-methoxyphenoxy)-1,3,5-triazin-2-yl]-L-leucinate	2.71	418
37	Methyl *N*-[4-(pentylamino)-6-(4-methoxyphenoxy)-1,3,5-triazin-2-yl]-L-leucinate	2.83	432

Example 38. Synthesis of Methyl *N*-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}glycinate (38).



Example 38

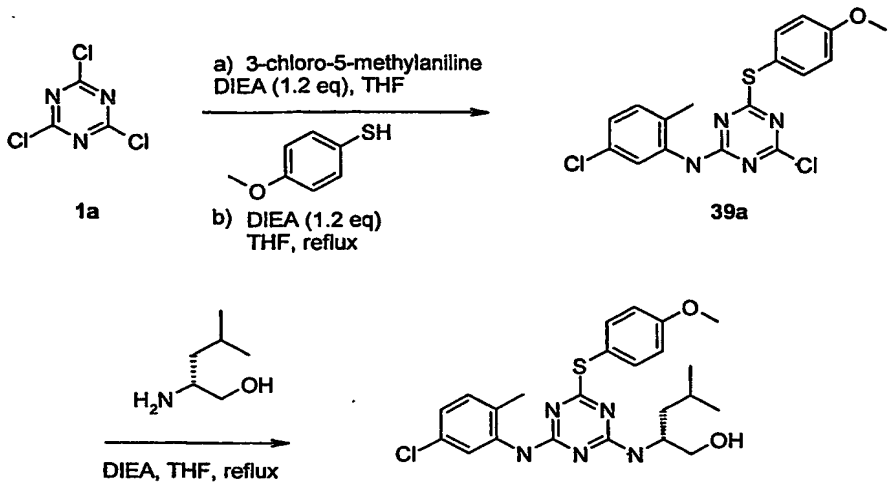
A portion of 4-chloro-*N*-(3-fluorophenyl)-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-amine **38a** (0.65 g, 1.7 mmol) was dissolved in DMF (10 mL) and to this was added PS-HOBT (1.00 g, 1.4 mmol), followed by DIEA (0.60 mL, 3.3 mmol). The suspension was carefully stirred at 90° C for 2h. The resin was filtered and washed with CH_2Cl_2 (3 x 100 mL), then Et_2O (1 x

100 mL) and dried *in vacuo* to give a yellow free-flowing resin **38b** (1.79 g). A portion of the resultant resin (0.200 g) was added to PS-DIEA (0.200 g, 4 mmol/g) in THF (1.5 mL). To this suspension was added glycine methyl ester hydrochloride and the mixture was heated to 160° C for five minutes in a Smithsynthesizer microwave reactor vessel. The reaction was filtered, washed with CH_2Cl_2, and the solvent was removed *in vacuo* to give the title compound, Example **38**, as a white foam (0.036 g). ^{1}H NMR δ (300 MHz, DMSO-*d6*, 300K) 3.59-3.62 (br s, 3H), 3.81 (s, 3H), 3.99 (br s, 2H), 6.72 (m, 1H), 7.01 (app t, 2H, J = 8.1 Hz), 7.16-7.24 (m, 3H), 7.44 (d, 1/2H, J= 8.1 Hz), 7.51 (d, 1/2H, J = 8.1 Hz), 7.92 (br s, 1H), 9.71 (br, s 1H). ^{1}H NMR (300 MHz, DMSO-*d6*, 363K) δ 3.62 (s, 3H), 3.81 (s, 3H), 3.94 (br s, 2H), 6.69 (app t, 1H, J = 9.0 Hz), 6.99 (d, 2H, J = 9.0 Hz); 7.14 (dd, 1H, J = 6.0, 7.5 Hz), 7.25 (br s, 1H), 7.45-7.51 (m, 3H), 9.36 (br, s 1H). APCI, *m/z* = 416 (M+1). LC/MS t_R = 2.62 min.

Synthesis of 4-Chloro-*N*-(3-fluorophenyl)-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-amine (38a).

To a stirred solution of cyanuric chloride (**1a**) (1.11 g, 6.0 mmol) in THF (50 mL) was added 3-fluoroaniline (0.43 mL, 6.0 mmol) and DIEA (0.62 mL, 6.6 mmol). The mixture was stirred for 1 hour, 4-methoxybenzenethiol (0.74 g, 6 mmol) was added and the solution heated to reflux overnight. The mixture was cooled to room temperature and the solvent removed *in vacuo*. The residual oil was partitioned between CH_2Cl_2 and 1N HCl (100 mL). The organic layer was separated, washed with NaCl (sat.) and dried over Na_2SO_4. The residual oil was chromatographed (10:1 hexanes/ethyl acetate) to give 4-chloro-*N*-(3-fluorophenyl)-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-amine **38a** (2.0 g, 92%). ^{1}H NMR (300 MHz, DMSO-*d6*, 300K) δ 6.72-6.77 (m, 2H), 6.99 (d, 2H, J = 8.4 Hz), 7.01-7.07 (m, 1H), 7.19-7.23 (m, 2H), 7.51 (d, 2H, J = 8.4 Hz). APCI, *m/z* = 363, 365 (M+1). LC/MS t_R = 2.87 min.

Example 39. (2*R*)-2-({4-[(5-Chloro-2-methylphenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}amino)-4-methylpentan-1-ol.



Example 39

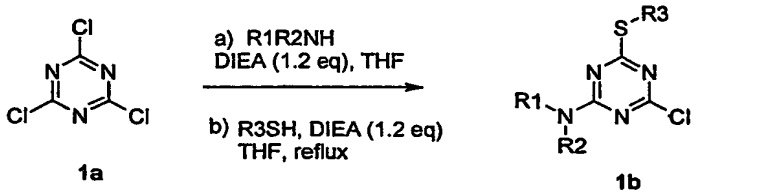
A portion of 4-chloro-*N*-(5-chloro-2-methylphenyl)-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-amine **39a** (0.325 g, 0.86 mmol) was dissolved in THF (10 mL) and to this was added DIEA (0.181 mL, 1.03 mmol) and 2-(R)-4-methylpentan-1-ol (0.10 g, 0.86 mmol). The solution was refluxed for 4h, cooled and the solvent removed in vacuo. The residual oil was chromatographed (SiO_2), using hexanes/ethyl acetate (80/20) to obtain the title compound **39** as a white foam (0.036 g, 8%). ^{1}H NMR (300 MHz, DMSO-*d6*, 363K) δ 0.76 (d, 3H, J = 6.6 Hz), 0.79 (d, 3H, J = 6.6 Hz), 1.26-1.29 (m, 3H), 2.13 (s, 3H), 3.29-3.32 (m, 2H), 3.77 (s, 3H), 4.15-4.18 (m, 1H), 6.60-6.62 (m, 1H), 6.78-6.80 (m, 1H), 6.90 (d, 2H, J = 8.7 Hz), 7.03 (dd, 1H, J = 2.0, 8.1 Hz), 7.13 (d, 1H, J = 8.1 Hz), 7.20–7.23 (m, 1H), 7.40-7.43 (m, 2H), 8.30-8.35 (m, 1H). APCI, *m/z* = 475 (M+1).

Synthesis of 4-chloro-*N*-(5-Chloro-2methylphenyl)-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-amine (39a).

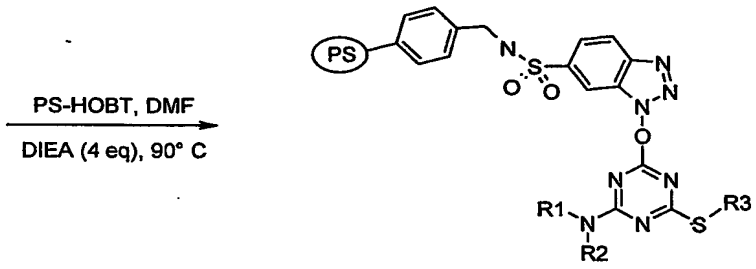
Synthesis of the title compound **39a** was analogous to the synthesis of 4-chloro-*N*-(3-fluorphenyl)-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-amine **38a**, except, 5-chloro-2-methyl aniline was used in place of 3-fluoroaniline.

By analogy, Examples 40-52 (Table 3) were prepared.

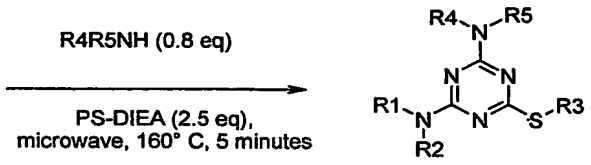
Method C-1



1a 1b

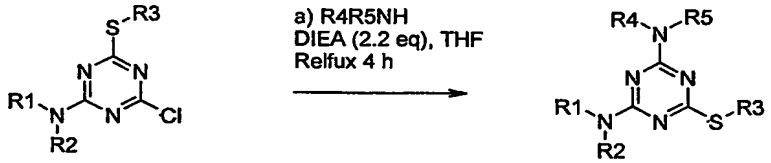


1c



1d

Method C-2



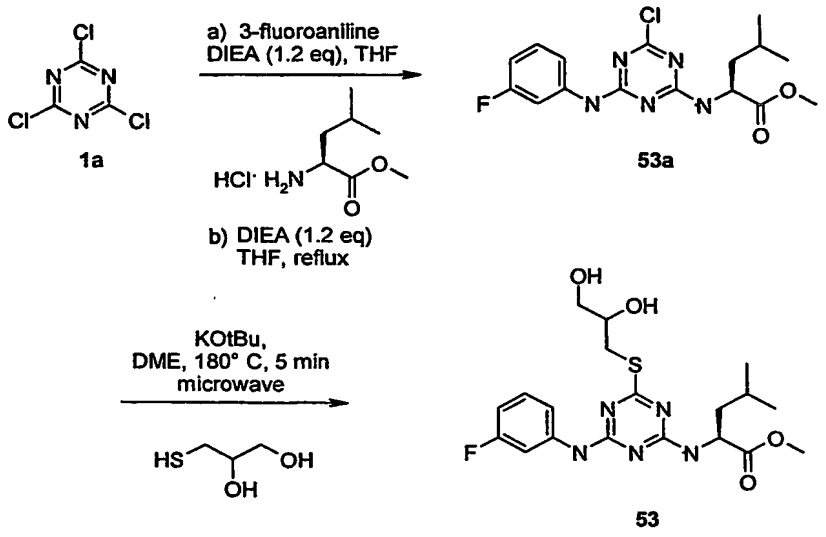
1b 1d

Table 3. Method C-1 and C-2, General Procedure for Examples 38-52.

Example (Method)	Name	LC/MS t_R (min)	MS APCI, *m/z* (M+1)
38 (C-1)	Methyl *N*-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}glycinate	2.62	416
39 (C-2)	(2*R*)-2-({4-[(5-Chloro-2-methylphenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}amino)-4-methylpentan-1-ol	=	475
40 (C-2)	Methyl *N*-{4-[(5-chloro-2-methylphenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-leucinate	3.14	503
41 (C-2)	Methyl *N*-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-leucinate	3.01	472
42 (C-1)	1-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}pyrrolidin-3-ol	2.49	414
43 (C-1)	N^2-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-leucinamide	2.64	457
44 (C-1)	N^2-(3-Fluorophenyl)-N^4-isopentyl-6-[(4-methoxyphenyl)thio]-1,3,5-triazine-2,4-diamine	3.07	414
45 (C-1)	(2*S*)-2-({4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}amino)-4-methylpentan-1-ol	2.76	444

46 (C-1)	Methyl *N*-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-phenylalaninate	3.04	506
47 (C-1)	2-({4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}amino)propan-1-ol	2.40	402
48 (C-1)	N^2-(2,2-Dimethoxyethyl)-N^4-(3-fluorophenyl)-6-[(4-methoxyphenyl)thio]-1,3,5-triazine-2,4-diamine	2.69	432 (5), 400 (100)
49 (C-1)	Ethyl *N*-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-β-alaninate	2.80	444
50 (C-1)	3-[{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}(methyl)amino]propanenitrile	2.87	411
51 (C-1)	Methyl *N*-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-alaninate	2.74	430
52 (C-1)	Methyl *N*-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-D-leucinate	3.01	472

Example 53. Methyl *N*-{4-[(2,3-dihydroxypropyl)thio]-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-L-leucinate (53).



1a 53a 53

To solution of 4-methoxybenzenethiol (0.40 mmol) dissolved in DME (1.5 mL) was added potassium *tert*-butoxide (0.048 g, 0.42 mmol). A portion of methyl *N*-{4-chloro-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-L-leucinate **53a** (0.150 g, 0.40 mmol) was added and the suspension was heated to 180° C for five minutes in a Smithsynthesizer microwave reactor vessel. The solvent was removed *in vacuo* and the residual oil was chromatographed (SiO_2), using a gradient of CH_2Cl_2/MeOH (100/0 to 90/10) to give the title compound **53** as a white foam (0.036 g). ^{1}H NMR (300 MHz, DMSO-*d6*, 363K) δ 0.89 (d, 3H, J= 6.0 Hz), 0.92 (d, 3H, J = 6.0 Hz), 1.61-1.77 (m, 3H), 3.10-3.14 (m, 1H), 3.31-3.35 (m, 1H), 3.38-3.43 (m, 2H), 3.62 (s, 3H), 3.71-3.74 (m, 1H), 4.20-4.25 (m, 1H), 4.50-4.55 (m, 2H), 6.74 (app t, 1H, J = 7.17 Hz), 7.25 (dd, 1H, J = 7.6, 15.6 Hz), 7.42-7.44 (m, 1H), 7.59-7.63 (m, 2H), 9.35-9.38 (m, 1H). APCI, *m/z* = 440 (M+1). LC/MS t_R = 2.31 min.

Alternatively, these reactions were carried out in refluxing THF or DME for 18 hours with comparable reaction yields to the ones stated above. Furthermore, bases such as K_2CO_3 or DIEA were used under these conditions with no noticeable loss in reaction yield.

Synthesis of Methyl *N*-{4-chloro-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-L-leucinate (53a).

To a stirred solution of cyanuric chloride **1a** (3.45 g, 18.7 mmol) in THF (80 mL) was added 3-fluoroaniline (1.82 mL, 18.7 mmol) and DIEA (4.89 mL, 28.0 mmol). The mixture was stirred for 1 hour, L-leucine methyl ester hydrochloride (3.39 g, 18.7 mmol) was added, followed by DIEA (4.89 mL, 28.0 mmol) and the solution heated to reflux for one hour. The mixture was cooled to room temperature and the solvent removed *in vacuo*. The residual oil

was partitioned between CH_2Cl_2 and 1N HCl (200 mL). The organic layer was separated, washed with $NaHCO_3$ (sat.), NaCl (sat.) and dried over Na_2SO_4. The residual oil was used as is without purification.

By analogy Examples 54-64 were prepared.

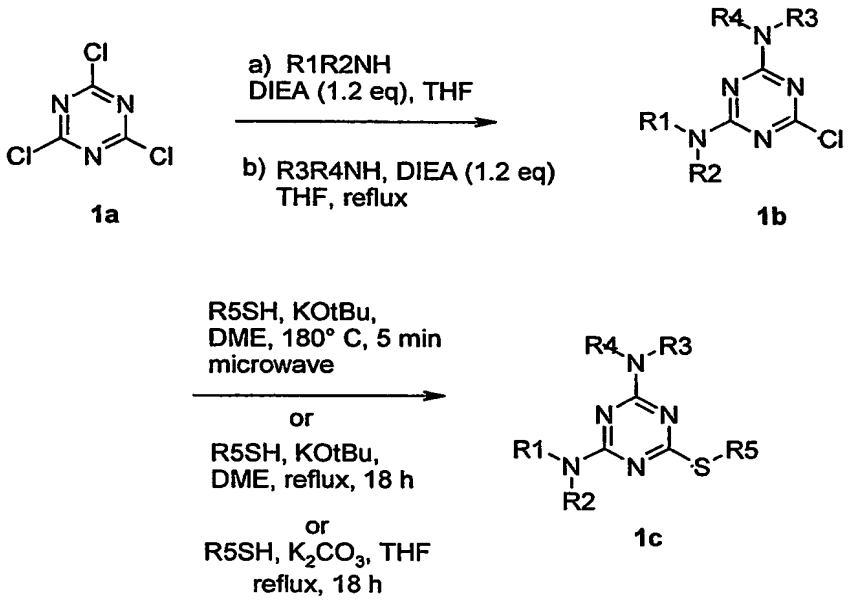
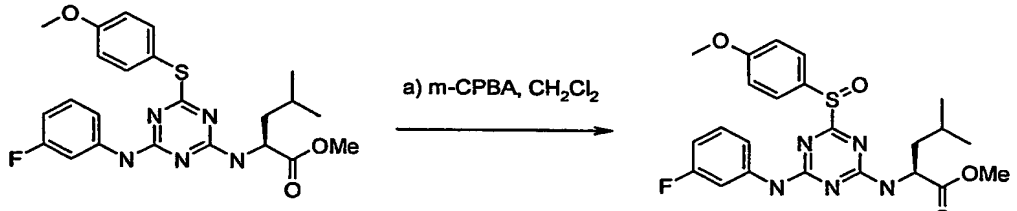


Table 4. Method D, General Procedure for Examples 53-64.

Example	Name	LC/MS t_R (min)	MS APCI, *m/z* (M+1)
53	Methyl *N*-{4-[(2,3-dihydroxypropyl)thio]-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-L-leucinate	2.31	440
54	Methyl *N*-{4-[(3-fluorophenyl)amino]-6-[(3-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-leucinate	3.11	472
55	Methyl *N*-{4-[(3-fluorophenyl)(methyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-leucinate	3.21	486
56	(2*R*)-2-({4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}amino)-4-methylpentan-1-ol	2.77	444
57	Methyl *N*-{4-[(3-fluorophenyl)amino]-6-[(2-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-leucinate	3.01	472
58	Methyl *N*-[4-[(3-fluorophenyl)amino]-6-(phenylthio)-1,3,5-triazin-2-yl]-L-leucinate	3.10	442
59	Methyl *N*-[4-[(3-fluorophenyl)amino]-6-(quinolin-2-ylthio)-1,3,5-triazin-2-yl]-L-leucinate	2.99	493
60	Methyl *N*-{4-[(4-aminophenyl)thio]-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-L-leucinate	2.58	457

61	Methyl *N*-{4-[(3-bromophenyl)thio]-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-L-leucinate	3.27	522, 524
62	Methyl *N*-[4-[(3-fluorophenyl)amino]-6-(pyrimidin-2-ylthio)-1,3,5-triazin-2-yl]-L-leucinate	2.61	444
63	Methyl *N*-{4-{[2-(dimethylamino)ethyl]thio}-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-L-leucinate	2.31	437
64	Methyl *N*-{4-({1-[2-(dimethylamino)ethyl]-1*H*-tetrazol-5-yl}thio)-6-[(3-fluorophenyl)amino]-1,3,5-triazin-2-yl}-L-leucinate	2.32	505

Example 65. Methyl *N*-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)sulfinyl]-1,3,5-triazin-2-yl}-L-leucinate (65).

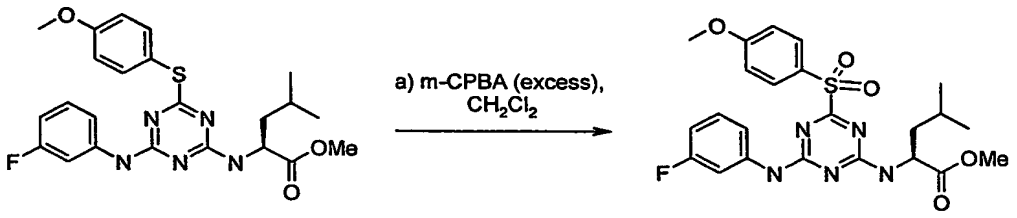


41 65

To a stirred solution of methyl *N*-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-leucinate **41** (0.500 g, 1.3 mmol) in CH_2Cl_2 at 0° C, was added *m*-chloroperoxybenzoic acid (0.300 g, 60%, 1 mmol). The reaction was stirred for 30 minutes, and then quenched with a 10% solution of $Na_2S_2O_3$. The organic layer was separated and then washed with $NaHCO_3$ (sat.), followed by NaCl (sat.). The solvent was dried over Na_2SO_4, filtered and concentrated to give a yellow oil. The material was chromatographed (SiO_2) using hexanes/ethyl acetate (80/20 to 50/50 gradient) to give the title compound **65** as a white solid (0.15 g, 23%). ^{1}H NMR (300 MHz, DMSO-*d6*, 363K) δ 0.88-0.91 (m, 6H), 1.60-1.73 (m, 3H), 3.58 (s, 3H), 3.80 (s, 3H), 4.47-4.52 (m, 1H), 6.79 (app t, 1H, J = 6.0 Hz), 7.08

(d, 1H, J = 7.8 Hz), 7.27 (dd, 1H, J = 7.5 Hz, 15.3 Hz), 7.40-7.45 (m, 1H), 7.63-7.69 (m, 3H), 8.30-8.35 (m, 1H), 9,96-9.99 (m, 1H). APCI, *m/z* = 488 (M+1). LC/MS t_R = 2.67 min.

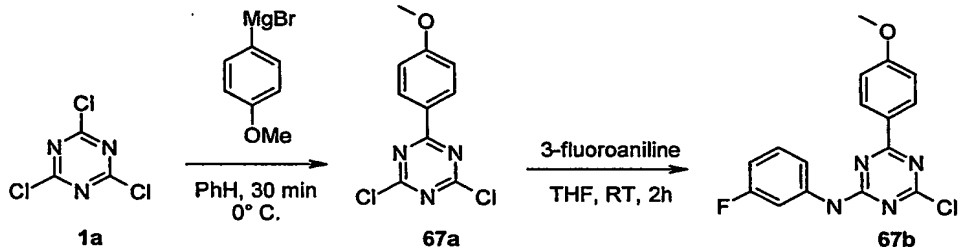
Example 66. Methyl *N*-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)sulfonyl]-1,3,5-triazin-2-yl}-L-leucinate (66).



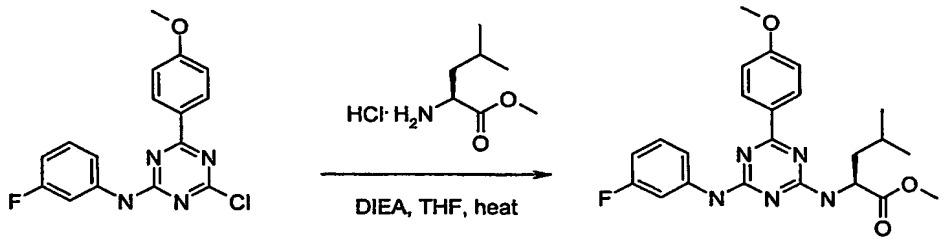
41 66

To a stirred solution of methyl *N*-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-leucinate **41** (0.500 g, 1.3 mmol) in CH_2Cl_2 at 0° C, was added *m*-chloroperoxybenzoic acid (0.800 g, 60%, 2.6 mmol). The reaction was stirred for 2 hours, and then quenched with a 10% solution of $Na_2S_2O_3$. The organic layer was separated and then washed with $NaHCO_3$ (sat.), followed by NaCl (sat.). The solvent was dried over Na_2SO_4, filtered and concentrated to give a yellow oil. The material was chromatographed (SiO_2) using hexanes/ethyl acetate (80/20) to give the title compound **66** as a white solid (0.045 g, 7%). APCI, *m/z* = 504 (M+1). LC/MS t_R = 2.86 min.

Example 67. Methyl *N*-[4-[(3-fluorophenyl)amino]-6-(4-methoxyphenyl)-1,3,5-triazin-2-yl]-L-leucinate (67).



1a 67a 67b



67b Example 67

To a stirred solution of 4-chloro-*N*-(3-fluorophenyl)-6-(4-methoxyphenyl)-1,3,5-triazin-2-amine **67b** (0.30 g, 0.9 mmol) in THF (10 mL) was added leucine methyl ester hydrochloride (0.16 g, 0.9 mmol) and DIEA (1.8 mmol) and the reaction was heated to 60° C for 18 hours. The reaction was concentrated and the residual oil chromatographed (SiO_2, hexanes/ethyl acetate, gradient 95/5 to 90/10) to give the title compound **67** as a white solid (0.065 g, 19%). ^{1}H NMR (300 MHz, $CDCl_3$, 300K) δ 0.94-0.96 (br s, 6H), 1.63-1.80 (m, 3H), 3.73 (s, 1.5H), 3.76 (s, 1.5H), 3.85 (s, 1.5H), 3.87 (s, 1.5H), 4.70-4.76 (m, 1H), 4.92-4.97 (m, 1H), 6.00-6.10 (m, 0.5H), 6.70-6.76 (m, 1H), 6.93-6.98 (m, 2H), 7.22-7.36 (m, 2H), 7.72-7.78 (m, 2H), 8.22 (d, 1H, J = 8.7 Hz), 8.36 (d, 1H, J = 8.7 Hz). APCI, *m/z* = 440 (M+1). LC/MS t_R = 3.10 min. Alternatively, the final compounds can be made in an analogous fashion to Example **1**, using the PS-HOBT resin.

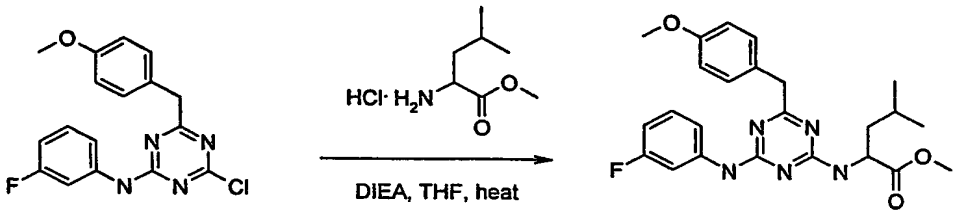
Synthesis of 4-chloro-*N*-(3-fluorophenyl)-6-(4-methoxyphenyl)-1,3,5-triazin-2-amine 67b.

To a cold (0° C), stirred solution of 2,4-dichloro-6-(4-methoxyphenyl)-1,3,5-triazine **67a** (1.28 g, 5.0 mmol) in THF (30 mL) was added DIEA (0.87 mL, 8.03 mmol), followed by 3-fluoroaniline (0.55 g, 5.0 mmol). The reaction was stirred for 2 hours at room temperature, concentrated and then partitioned between ethyl acetate (100 mL) and 1 N HCl (100 mL). The organic layer was washed with NaCl (sat.), dried and the solvent removed to give a tan solid (1.4 g, 85%). The material was used in the next reaction without further purification.

Synthesis of 2,4-dichloro-6-(4-methoxyphenyl)-1,3,5-triazine 67a.

To a cold (0° C), stirred solution of cyanuric chloride **1a** (1.09 g, 5.8 mmol) in benzene (20 mL) was slowly added 4-methoxyphenylmagnesium bromide (14.13 mL, 0.5 M in ether, 5.0 mmol). The reaction was stirred for 30 minutes at 0 °C, and then quenched with NH_4Cl (sat.) (20 mL). The reaction was diluted with diethyl ether (100 mL), washed with NaCl (sat.), and then dried over $MgSO_4$. The volatiles were removed to give a colorless oil (1.27 g, 85%). The material was used without further purification in the next reaction.

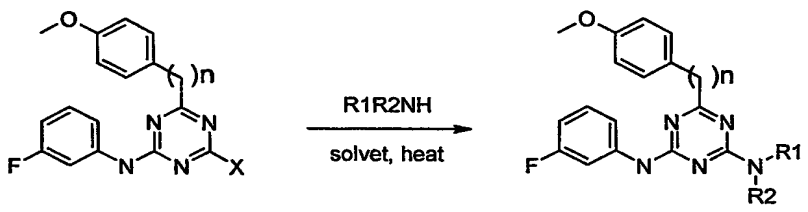
Example 68. Synthesis of methyl *N*-[4-[(3-fluorophenyl)amino]-6-(4-methoxybenzyl)-1,3,5-triazin-2-yl]-L-leucinate (68).



68a 68

The title compound was prepared in analogous fashion to methyl *N*-[4-[(3-fluorophenyl)amino]-6-(4-methoxyphenyl)-1,3,5-triazin-2-yl]-L-leucinate **67**, except 4-methoxybenzyl magnesium chloride was used as the starting Grignard reagent. See Table 5 for analytical data.

Examples 69-71 were prepared in analogous fashion to Example 1, using HOBT resin.



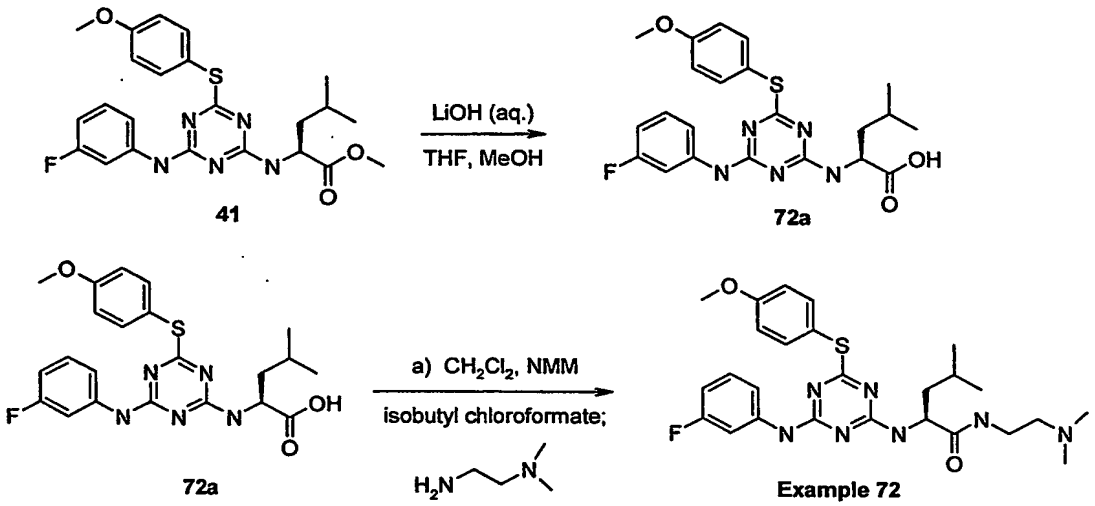
X = Cl or HOBT resin

n = 0,1

Table 5. Method E, General Procedure for Examples 67-71

Example	Name	LC/MS t_R (min)	MS APCI, *m/z* (M+1)
67	Methyl *N*-[4-[(3-fluorophenyl)amino]-6-(4-methoxyphenyl)-1,3,5-triazin-2-yl]-L-leucinate	3.10	440
68	Methyl *N*-[4-[(3-fluorophenyl)amino]-6-(4-methoxybenzyl)-1,3,5-triazin-2-yl]leucinate	2.68	454
69	Methyl *N*-[4-[(3-fluorophenyl)amino]-6-(4-methoxybenzyl)-1,3,5-triazin-2-yl]glycinate	2.23	398
70	(2*S*)-2-{[4-[(3-Fluorophenyl)amino]-6-(4-methoxybenzyl)-1,3,5-triazin-2-yl]amino}-4-methylpentan-1-ol	2.34	426
71	N^2-Benzyl-N^4-(3-fluorophenyl)-6-(4-methoxybenzyl)-1,3,5-triazine-2,4-diamine	2.53	416

Example 72. N^1-[2-(Dimethylamino)ethyl]-N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-leucinamide (72).



To a cold (-15° C), stirred solution of *N*-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-leucine **72a** (0.100 g, 0.21 mmol) dissolved in DMF (1.5 mL) or CH_2Cl_2 was added N-methyl morpholine (0.027 mL, 0.24 mmol), followed by isobutyl chloroformate (0.032 mL, 0.24 mmol). The reaction was stirred for five minutes, then N,N-dimethyl ethlyenediamine (0.026 mL, 0.24 mmol) was added. The reaction was stirred overnight, concentrated and chromatographed (SiO_2, CH_2Cl_2/MeOH, gradient, 100/0 to 95/5) to give the title compound **72** as a white foam (0.020 g, 17%). ^{1}H NMR (300 MHz, $CDCl_3$, 300K) δ 0.79-.89 (m, 6H), 1.50-1.59 (m, 3H), 2.09 (s, 3H), 2.15 (s, 3H), 2.25-2.30 (m, 2H), 3.09-3.15 (m, 2H), 3.55 (t, 1H, J = 4.8 Hz), 3.81 (br s, 3H), 6.69-6.74 (br s, 1H), 7.00-7.05 (m, 2H), 7.10-7.15 (m, 1H), 7.25-7.30 (m, 1H), 7.48-7.52 (m, 2H), 7.56-7.68 (m, 1H), 9.58-9.62 (m, 1H). APCI, *m/z* = 528 (M+1). LC/MS t_R = 2.48.

<u>*N*-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-leucine (72a).</u>

To a stirred solution of methyl *N*-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-leucinate **41** (10.1 g, 21.4 mmol) in THF (50 mL), MeOH (50 mL) and H_2O (50 mL) was added LiOH (2.25 g, 53.5 mmol). The reaction was stirred at room temperature for 2 hours. The material was concentrated and then partitioned between 1 N HCl and CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated to give the title compound **72a** as a white solid (9.4 g, 96%). APCI, *m/z* = 472 (M+1). LC/MS t_R = 3.01.

By analogy Examples 73-90 were prepared from *N*-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-leucine (**72a**).

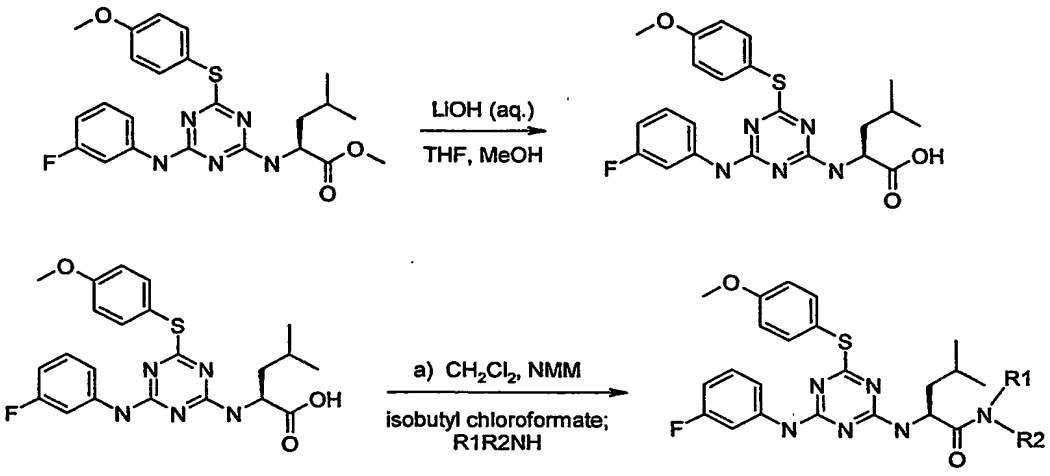

LiOH (aq.)
THF, MeOH
a) CH_2Cl_2, NMM
isobutyl chloroformate;
R1R2NH

Table 6. Method F, General Procedure for Examples 72-90

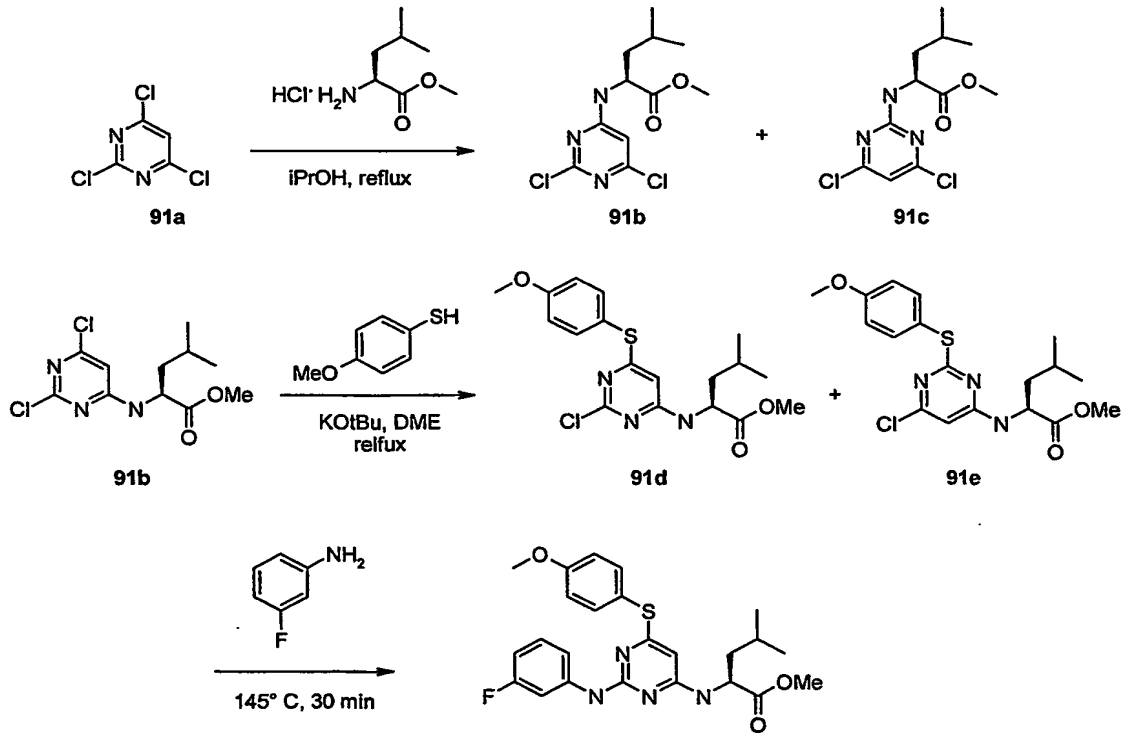
Example	Name	MS APCI, *m/z* (M+1)	LC/MS t_R (min)
72	N^1-[2-(Dimethylamino)ethyl]-N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-leucinamide	528	2.48
73	N^2-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-N^1-(tetrahydrofuran-2-ylmethyl)-L-leucinamide	541	2.79
74	N^2-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-N^1-(2-morpholin-4-ylethyl)-L-leucinamide	570	2.44
75	N^1-{2-[(*tert*-Butoxycarbonyl)amino]ethyl}-N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-leucinamide	600	2.94
76	N^2-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-N^1-(pyridin-3-ylmethyl)-L-leucinamide	548	2.43

77	N^1-(3,5-Difluorobenzyl)-N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-leucinamide	583	3.08
78	N^2-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-N^1-(2-furylmethyl)-L-leucinamide	537	3.19
79	N^2-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-N^1-[3-(2-oxopyrrolidin-1-yl)propyl]-L-leucinamide	582	2.89
80	N^2-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-N^1-(3-methoxybenzyl)-L-leucinamide	577	3.07
81	N^2-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-N^1-(2-piperidin-1-ylethyl)-L-leucinamide	568	2.59
82	N^2-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-N^1-[2-(2-hydroxyethoxy)ethyl]-L-leucinamide	545	2.58

83	N^2-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-N^1-phenyl-L-leucinamide	533	3.14
84	N^2-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-N^1-propyl-L-leucinamide	499	2.94
85	N^2-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-N^1-(2-pyrrolidin-1-ylethyl)-L-leucinamide	554	2.52
86	N^2-(3-Fluorophenyl)-6-[(4-methoxyphenyl)thio]-N^4-[(1*S*)-3-methyl-1-(morpholin-4-ylcarbonyl)butyl]-1,3,5-triazine-2,4-diamine	527	2.89
87	N^1-{2-[4-(Aminosulfonyl)phenyl]ethyl}-N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-L-leucinamide	640	2.79
88	N^2-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-N^1-[2-(1-methylpyrrolidin-2-yl)ethyl]-L-leucinamide	568	2.53

89	N^2-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-N^1-(3-methoxypropyl)-L-leucinamide	529	3.07
90	N^2-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]-1,3,5-triazin-2-yl}-N^1-(pyridin-2-ylmethyl)-L-leucinamide	548	2.80

Example 91: Methyl *N*-{2-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-4-yl}-L-leucinate (91).



To an equimolar mixture of methyl *N*-{2-chloro-6-[(4-methoxyphenyl)thio]pyrimidin-4-yl}-L-leucinate **91d** and methyl *N*-{6-chloro-2-[(4-methoxyphenyl)thio]pyrimidin-4-yl}-L-

leucinate **91e** (0.412 g, 1.04 mmol) was added 3-fluoroaniline (0.75 mL, 7.5 mmol) and the mixture heated to 145° C for 30 minutes. The reaction was cooled and chromatographed (SiO_2) using hexanes/ethyl acetate (gradient 90/10-70/30) to give the title compound **91** as a white foam (0.036 g, 14%). ^{1}H NMR (300 MHz, $CDCl_3$, 300K) δ 0.92 (d, 3H, J = 6.0 Hz), 0.94 (d, 3H, J = 6.0 Hz), 1.55-1.66 (m, 3H), 3.69 (s, 3H), 3.87 (s, 3H), 4.69-4.71 (m, 2H), 5.36 (s, 1H), 6.63 (app t, 1H, J = 6.3 Hz), 6.84 (s, 1H), 6.97 (d, 2H, J = 8.7 Hz), 7.14 (dd, 1H, J = 8.4, 15 Hz), 7.48-7.55 (m, 3H). APCI, *m/z* = 471 (M+1). LC/MS t_R = 3.06 min. Assignment of this isomer was established using NOE studies.

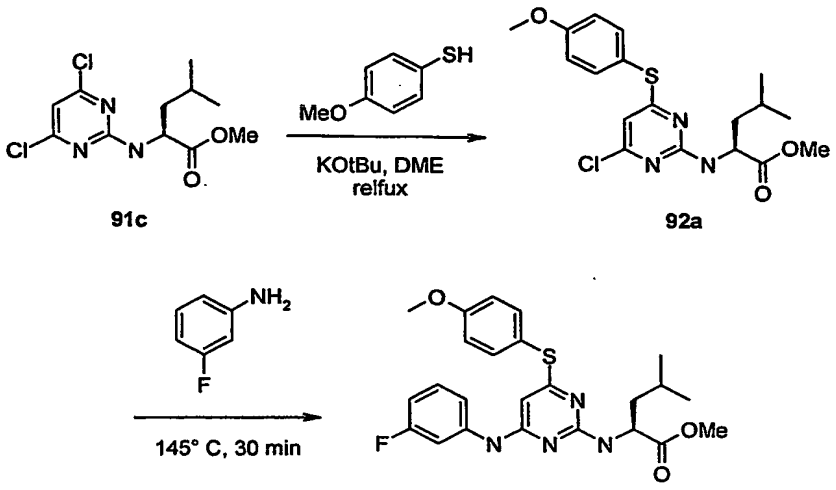
Synthesis of Methyl *N*-{2-chloro-6-[(4-methoxyphenyl)thio]pyrimidin-4-yl}-L-leucinate (91d) and methyl *N*-{6-chloro-2-[(4-methoxyphenyl)thio]pyrimidin-4-yl}-L-leucinate (91e).

To a solution of 4-methoxybenzenethiol (0.577 mL, 4.69 mmol) in DME (10 mL) was added potassium *tert*-butoxide (0.534 g, 4.69 mmol) and the reaction stirred for five minutes. To this was added methyl *N*-(2,6-dichloropyrimidin-4-yl)-L-leucinate **91b** (1.37 g, 4.69 mmol). The mixture was refluxed for one hour, cooled and then the solvents removed *in vacuo*. The residual oil was chromatographed to give a 1:1 mixture of the title compounds. The mixture was used without further purification.

Synthesis of Methyl *N*-(2,6-dichloropyrimidin-4-yl)-L-leucinate (91b) and methyl *N*-(4,6-dichloropyrimidin-2-yl)-L-leucinate (91c).

To a stirred solution of 2,4,6 –trichloropyrimdine **91a** (1.50 g, 8.2 mmol) in *i*-PrOH (30 mL) was added leucine methyl ester hydrochloride (1.5 g, 8.2 mmol) and DIEA (16.4 mmol) and the mixture was refluxed for 1 hour. The solvent was removed *in vacuo* and the residual oil chromatographed (SiO_2) using hexanes/ethyl acetate gradient (100/0 to 90/10) to give methyl *N*-(4,6-dichloropyrimidin-2-yl)-L-leucinate **91c** (0.500 g, 21%) and methyl *N*-(2,6-dichloropyrimidin-4-yl)-L-leucinate **91b** (1.3 g, 54%) as white foams.

Example 92. Methyl *N*-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-L-leucinate (92).

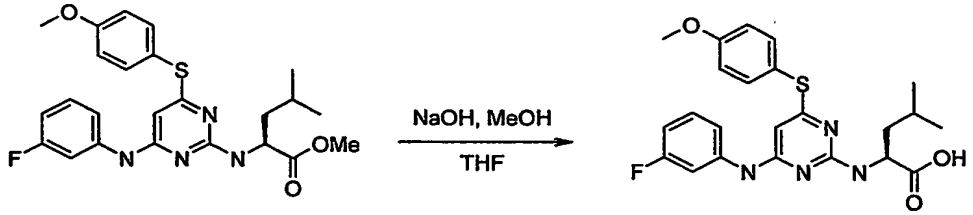


91c 92a

Example 92

To a solution of 4-methoxybenzenethiol (0.197 g, 1.41 mmol) in DME (3 mL) was added potassium tert-butoxide (0.160 g, 1.41 mmol) and the reaction stirred for five minutes. To this was added methyl *N*-(4,6-dichloropyrimidin-2-yl)-L-leucinate **91c** (0.410 g, 1.41 mmol). The mixture was refluxed for one hour, cooled and then the solvents removed *in vacuo*. The residual oil was partitioned between CH_2Cl_2 and NaCl (sat), and then the organic layer was collected and dried over Na_2SO_4. The crude oil was dissolved in 3-fluoroaniline (1.0 mL) and the reaction heated to 145° C for 30 minutes. The reaction was cooled and chromatographed (SiO_2) using hexanes/ethyl acetate (100/0 to 80/20 gradient) to isolate the title compound **92** as a white solid (0.138 g, 20%). ^{1}H NMR (300 MHz, $CDCl_3$, 300K) δ 0.92 (d, 3H, J = 6.0 Hz), 0.94 (d, 3H, J = 6.0 Hz), 1.59-1.65 (m, 2H), 1.70-1.79 (m, 1H), 3.69 (s, 3H), 3.85 (s, 3H), 4.60-4.64 (m, 1H), 5.16 (d, 1H, J = 8.1 Hz), 5.40 (s, 1H), 6.25 (s, 1H), 6.70 (app t, 1H, J = 6.3 Hz), 6.85 (d, 1H, J = 8.1 Hz), 6.95 (d, 2H, J = 8.7 Hz), 7.12-7.17 (m, 2H), 7.50 (d, 1H, J = 8.7 Hz). APCI, *m/z* = 471 (M+1). LC/MS t_R = 2.84 min. Assignment of this isomer was confirmed by NOE studies.

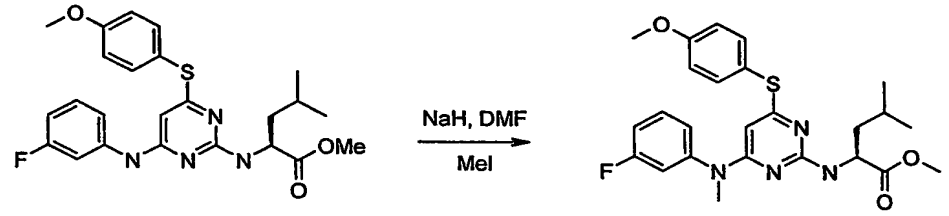
Example 93. *N*-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-leucine (93).



92 Example 93

To a stirred solution of methyl *N*-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-L-leucinate **92** (0.100 g, 0.21 mmol) in MeOH (1 mL) was added THF (1 mL) and 1 N NaOH (0.30 mL). The reaction was stirred for 2 hours, then quenched with 1 N HCl (1 mL). The volatiles were removed *in vacuo* and the material dried by azeotropic removal using toluene. The residual material was recrystallized using hexanes/ethyl acetate (80/20) to give the title compound **93** as a white solid (0.058 g, 61%). ^{1}H NMR (300 MHz, DMSO-*d6*, 300K) δ 0.85 (d, 3H, J = 6.0 Hz), 0.93 (d, 3H, J = 6.0 Hz), 1.58-1.74 (m, 3H), 3.83 (s, 3H), 4.34 (m, 1H), 5.45 (br s, 1H), 6.70-6.77 (m, 1H), 7.10-7.15 (m, 2H), 7.19-7.26 (m, 2H), 7.50-7.56 (m, 3H). APCI, *m/z* = 457 (M+1). LC/MS t_R = 2.50 min.

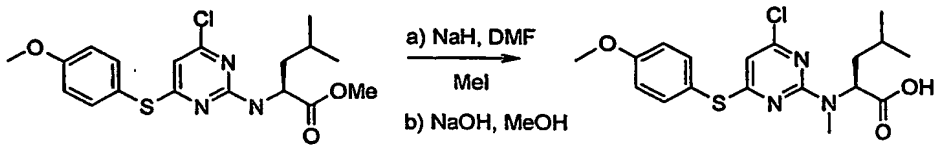
Example 94. *N*-{4-[(3-Fluorophenyl)(methyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-L-leucine (94).



92 Example 94

To a cold (0° C) stirred solution of methyl *N*-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-L-leucinate **92** (0.100 g, 0.21 mmol) in THF was added NaH (60% in mineral oil, 0.008 g, 0.21 mmol) and the reaction stirred for five minutes. To this was added methyl iodide (0.013 mL, 0.21 mmol) and the reaction stirred for 30 minutes. The reaction was diluted with CH_2Cl_2 and washed with NaCl (20 mL) (sat) containing five drops of 1N HCl. The organic layers were collected and dried over Na_2SO_4 and the solvents removed *in vacuo*. The residual oil was chromatographed to give the title compound **94** as a white foam (0.18 g, 18%). ^{1}H NMR (300 MHz, $CDCl_3$, 300K) δ 0.92 (d, 3H, J = 6.0 Hz), 0.95 (d, 3H, J = 6.0 Hz), 1.62-1.64 (m, 2H), 1.73-1.77 (m, 1H), 3.30 (s, 3H), 3.69 (s, 3H), 3.80 (s, 3H), 4.56-4.59 (m, 1H), 5.06-5.11 (m, 2H), 6.69-6.84 (m, 4H), 7.12-7.20 (m, 2H), 7.37 (d, 2H, J = 8.1 Hz). APCI, *m/z* = 485 (M+1). LC/MS t_R = 3.13 min.

Example 95. *N*-{4-Chloro-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-*N*-methyl-leucine (95).



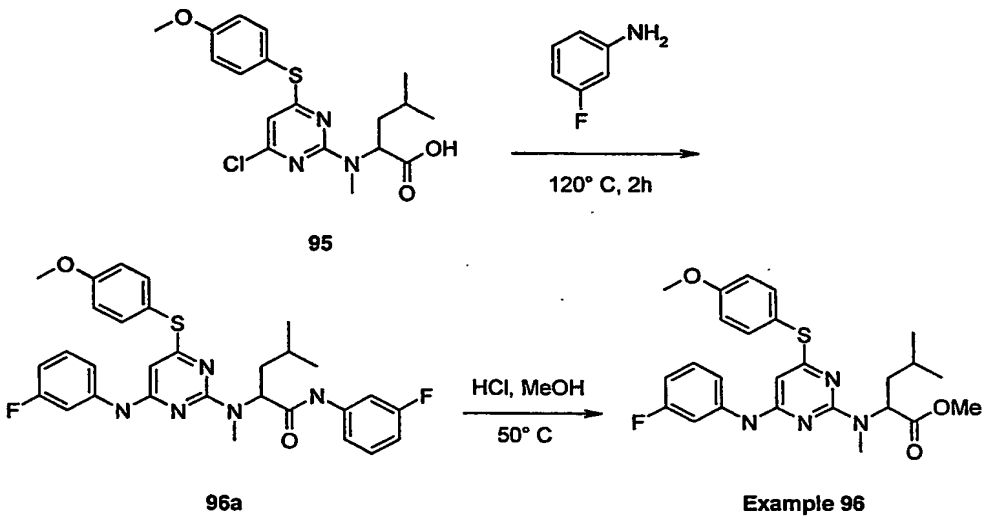
92a Example 95

To a stirred solution of methyl *N*-{4-chloro-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-*N*-methyl-L-leucinate (0.200 g, 0.48 mmol) in MeOH (1 mL) was added tetrahydrofuran (1 mL) and 1 N NaOH (1.4 mL, 1.4 mmol). The reaction was stirred at 50° C for 1h. The volatiles were removed and the reaction was quenched with 1 N HCl (1.6 mL). The aqueous phase was extracted with CH_2Cl_2 and then washed with NaCl (sat.). The volatiles were removed and the resultant oil was chromatographed (SiO_2, CH_2Cl_2/MeOH, gradient 100/0 to 90/10) to give **95** as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$, 300K) δ 0.85 (br s, 3H), 0.91 (d, 1H, J = 6.0 Hz), 1.45-1.49 (m, 1H), 1.73-1.78 (m, 2H), 3.02 (s, 3H), 3.85 (s, 3H), 5.26-5.32 (m, 1H), 6.10-6.14 (m, 1H), 6.95 (d, 2H, J = 8.7 Hz), 7.46 (d, 2H, J = 8.7 Hz). APCI, *m/z* = 396 (M+1). LC/MS t_R = 3.32 min.

Synthesis of Methyl *N*-{4-chloro-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-*N*-methyl-L-leucinate.

To a cold (0° C), stirred solution of methyl *N*-{4-chloro-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-L-leucinate **92a** (0.210 g, 0.50 mmol) in DMF (0.40 mL) was added sodium hydride (0.022 g, 60% in mineral oil, 0.51 mmol). The reaction was stirred for five minutes, and methyl iodide (0.034 mL, 0.51 mmol) was added. The reaction was stirred for thirty minutes, and then diluted with CH_2Cl_2 (50 mL). The organic layers were washed with NaCl (sat. 50 mL) containing two drops of 1N HCl. The organic layer was separated and dried over Na_2SO_4, and then the residual oil chromatographed (SiO_2, hexanes/ethyl acetate, 90/10) to give a white foam (0.135 g, 64%). The resultant material was used as is in the next reaction.

Example 96. Methyl *N*-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-*N*-methylleucinate (96).

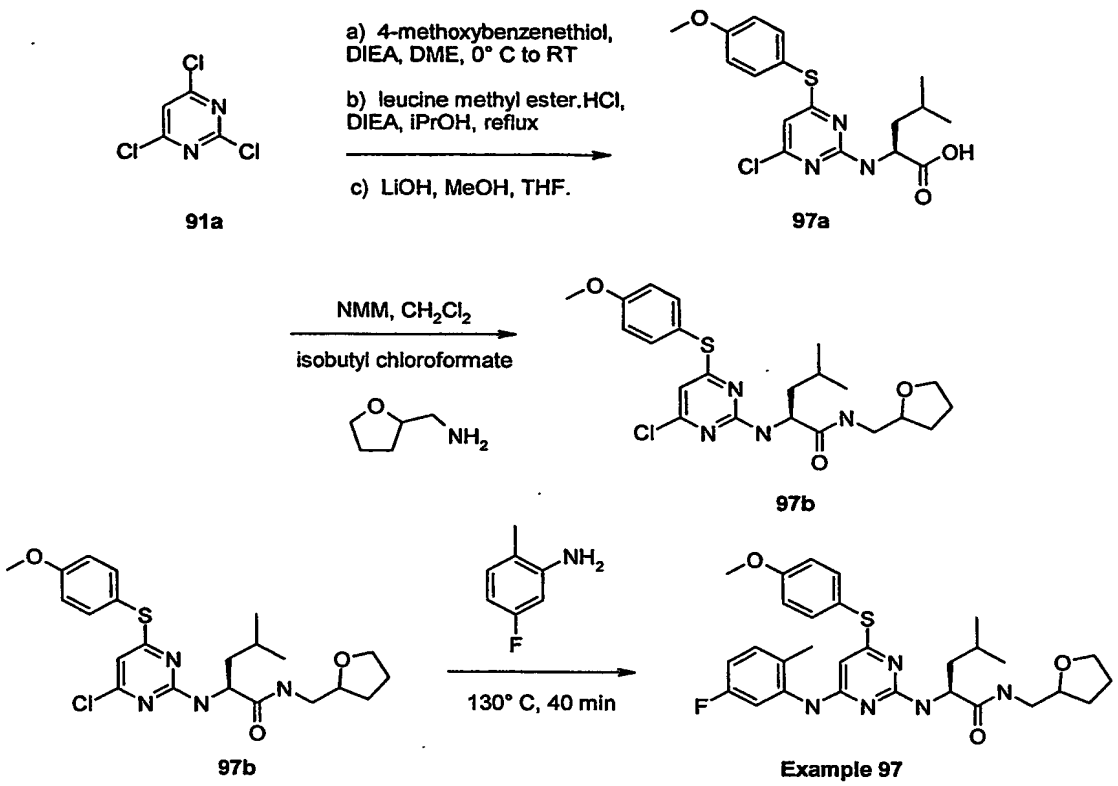


To a stirred solution of N^1-(3-fluorophenyl)-N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^2-methylleucinamide **96a** (0.080, 0.14 mmol) in MeOH (2 mL) was added HCl (conc, 2mL) and the reaction stirred at 60° C for 1h. The reaction was extracted with CH_2Cl_2, washed with H_2O, NaCl (sat.) and dried over Na_2SO_4. Removal of the solvent and chromatography (hexanes/ethyl acetate 90/10) gave the title compound **96** as a white solid (0.016 g, 23%). ^{1}H NMR (300 MHz, $CDCl_3$, 300K) δ 0.86 (d, 3H, J = 6.0 Hz), 0.92 (d, 3H, J = 6.0 Hz), 1.73-1.78 (m, 3H), 3.02 (s, 3H), 3.68 (s, 3H), 3.85 (s, 3H), 5.45 (br s, 2H), 6.24 (br s, 1H), 6.69 (app t, J = 8.1 Hz), 6.92-6.95 (m, 4H), 7.17 (dd, 1H, J = 8.4, 15 Hz), 7.50 (d, 2H, J = 8.1 Hz). APCI, *m/z* = 485 (M+1). LC/MS t_R = 3.43 min.

Synthesis of N^1-(3-Fluorophenyl)-N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^2-methylleucinamide (96a).

A solution of *N*-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-*N*-methylleucine **95** (0.100 g, 0.22 mmol) in 3-fluoroaniline (0.250 mL) was heated to 120° C for 2h. The reaction was cooled and partitioned between CH_2Cl_2 and 1N HCl. The organics were collected and washed with NaCl (sat.) and dried over Na_2SO_4. The solvent was removed to give a pale yellow foam which was used without purification in the next reaction. APCI, *m/z* = 564 (M+1). LC/MS t_R = 3.56 min.

Example 97. N^2-{4-[(5-Fluoro-2-methylphenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-(tetrahydrofuran-2-ylmethyl)-L-leucinamide (97).



A solution of N^2-{4-chloro-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-(tetrahydrofuran-2-ylmethyl)-L-leucinamide **97b** (0.126 g, 0.20 mmol) in 3-fluoro-6-methyl aniline (0.169 g, 1.35 mmol) was heated to 130° C for 40 minutes. The reaction was cooled and then chromatographed (SiO_2, $CHCl_3$/MeOH, gradient, 100/0 to 98/2) to give the title compound as white foam (0.022 g, 14%). ^{1}H NMR (300 MHz, $CDCl_3$, 300K) δ 0.89-0.96 (m, 6H), 1.75-1.92 (m, 3H), 2.12 (br s, 3H), 3.20-3.26 (m, 1H), 3.38-3.43 (m, 1H), 3.66-3.71 (m, 2H), 3.77-3.79 (m, 1H), 3.83 (s, 1H), 3.88-3.93 (m, 1H), 4.30-4.38 (m, 1H), 5.00-5.10 (m, 1H), 5.37 (d, 1H, J = 12.6 Hz), 6.24-6.30 (m, 1H), 6.63-6.74 (m, 2H), 6.92 (d, 2H, J = 8.1 Hz), 7.07 (app t, 1H, J = 6.3 Hz), 7.43-7.48 (m, 2H). APCI, *m/z* 578 (M+1). LC/MS t_R = 2.90 min.

Synthesis of N^2-{4-Chloro-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-(tetrahydrofuran-2-ylmethyl)-L-leucinamide (97b).

To a cold (-15° C), stirred solution of *N*-{4-chloro-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-L-leucine **97a** (0.31 g, 0.80 mmol) in CH_2Cl_2 was added N-methyl morpholine (0.09 mL, 0.83 mmol) followed by isobutyl chloroformate (0.120 mL, 0.90 mmol). After five minutes, tetrahydrofurfuryl amine (0.08 mL, 0.86 mmol) was added and the mixture stirred for 1 hour.

The reaction was concentrated and chromatographed (SiO_2, hexane/ethyl acetate, gradient, 100/0 to 70/30) to give the title compound as a white foam (0.157 g, 40%).

Synthesis of *N*-{4-Chloro-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-L-leucine (97a).

To a stirred solution of methyl *N*-{4-chloro-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-L-leucinate (0.377 g, 0.90 mmol) in MeOH (2.3 mL), THF (2.3 mL) was added an aqueous solution of LiOH (0.08 g in 1.15 mL H_2O, 1.80 mmol). The reaction was stirred at room temperature for 1.5 hours and then concentrated. To the residual oil was added 1 N HCl (pH < 7) and the reaction was partitioned between CH_2Cl_2 and H_2O. The organic layer was dried and the solvent evaporated to give a white solid (0.32 g, 90%).

Synthesis of Methyl *N*-{4-chloro-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-L-leucinate.

To a stirred solution of 2,4-dichloro-6-[(4-methoxyphenyl)thio]pyrimidine (15.65 g, 54.5 mmol) in iPrOH (200 mL) was added leucine methyl ester hydrochloride (11.3 g, 62.7 mmol) and DIEA (22.79 mL, 131 mmol). The mixture was refluxed for 3.5 hours to give a 1:1 mixture of isomers and then the reaction was concentrated. The residual oil was partitioned between CH_2Cl_2 (500 mL) and 1N HCl (3 x 100 mL). A portion of the material was chromatographed (11 g) SiO_2, hexanes/ethyl acetate, gradient, 100/0 to 80/20 over 38 minutes at 35 ml/min to give the title compound (4.35 g, 23%) as a white solid.

Synthesis of 2,4-Dichloro-6-[(4-methoxyphenyl)thio]pyrimidine.

To a cold (-15° C), stirred solution of 2, 4, 6-trichloropyrimidine **91a** (10.0 g, 54.5 mmol) in DME (40 mL) was added 4-methoxybenzenethiol (7.64 g, 54.5 mmol) and DIEA (7.05 g, 54.5 mmol). The reaction was stirred at room temperature for 1 hour and then concentrated. The reaction was partitioned between CH_2Cl_2 (100 mL) and 1 N HCl (50 mL) and then the organic layer was dried over $MgSO_4$. The material was then concentrated to give a yellow oil (15.65 g, 100%).

Examples 98-101, 135 and 136 were prepared in analogous fashion to Example 97.

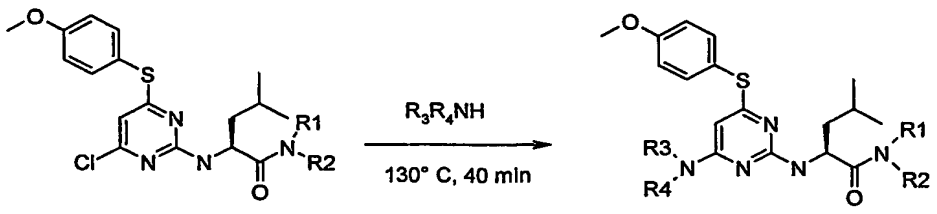
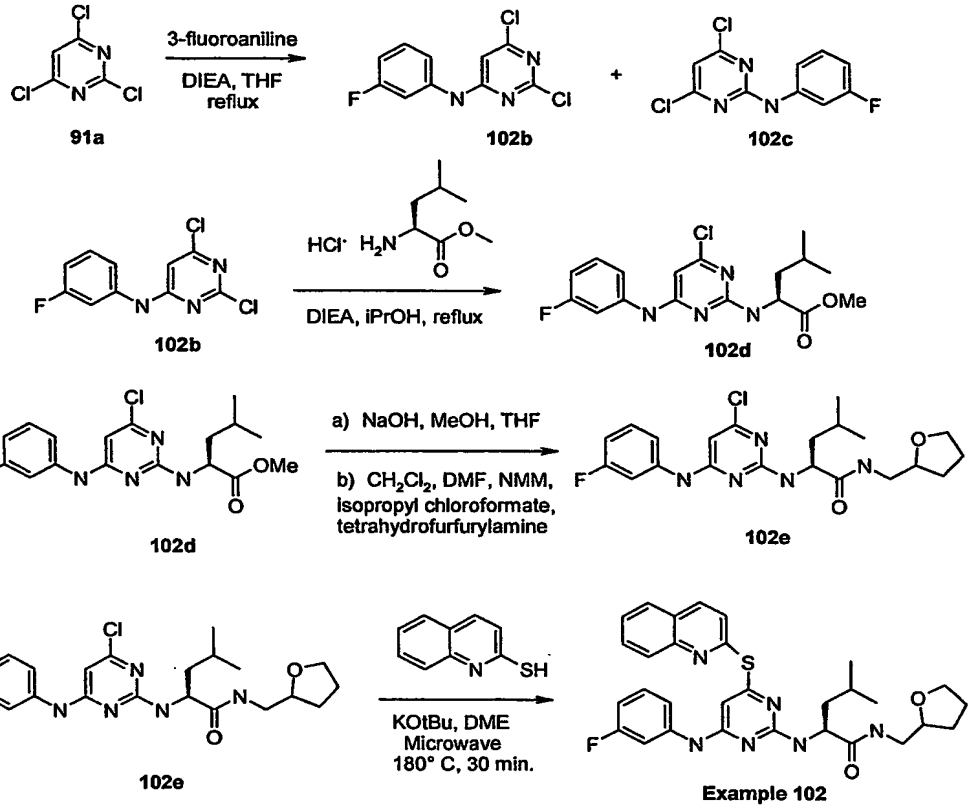


Table 7. Method F, General Procedure for Examples 97-101,135 and 136.

Example	Name	LC/MS t_R (min)	MS APCI, *m/z* (M+1)
97	N^2-{4-[(5-Fluoro-2-methylphenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-(tetrahydrofuran-2-ylmethyl)-L-leucinamide	2.90	554
98	N^2-{4-[(5-Fluoro-2-methylphenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-propyl-L-leucinamide	2.94	512
99	N^2-{4-[(3-Cyanophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-(tetrahydrofuran-2-ylmethyl)-L-leucinamide	2.77	547
100	N^2-{4-[(5-Chloro-2-methylphenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-(tetrahydrofuran-2-ylmethyl)-L-leucinamide	2.85	570
101	N^2-{4-[(3,5-Difluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-(tetrahydrofuran-2-ylmethyl)-L-leucinamide	2.40	557
135	***138***	2.63	537

136	N^2-{4-[(2-Pyridyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-(tetrahydrofuran-2-ylmethyl)-L-leucinamide	2.44	522

Example 102. N^2-[4-[(3-Fluorophenyl)amino]-6-(quinolin-2-ylthio)pyrimidin-2-yl]-N^1-(tetrahydrofuran-2-ylmethyl)-L-leucinamide (102).



To a solution of 2-quinolinethiol (0.038 g, 0.23 mmol) in DME (2 mL) was added potassium *tert*-butoxide (0.027 g, 0.23 mmol) and the reaction stirred for five minutes. To this was added N^2-{4-chloro-6-[(3-fluorophenyl)amino]pyrimidin-2-yl}-N^1-(tetrahydrofuran-2-ylmethyl)-L-leucinamide **102e** (0.100 g, 0.22 mmol) and the reaction vessel heated to 180° C for 15 minutes in a Smithsynthesizer microwave reactor. The reaction was cooled, and another portion of 2-quinolinethiol (0.076 g, 0.46 mmol) and potassium *tert*-butoxide (0.054 g, 0.46 mmol) was added. The reaction was again heated to 180° C for 15 minutes using microwave heating. The solvent was removed *in vacuo*, and the material chromatographed (SiO_2, $CHCl_3$/2N NH_3 in MeOH, gradient, 100/0 to 98/2 to give **102** as a white solid (0.022 g,

17%). ^{1}H NMR (300 MHz, $CDCl_3$, 300K) δ 0.90-1.00 (m, 6H), 1.59-1.65 (m, 3H), 1.73-1.90 (m, 4H), 3.13-3.18 (m, 1H), 3.44-3.49 (m, 1H), 3.68-3.79 (m, 2H), 3.88-3.93 (m, 1H), 4.27-4.32 (m, 1H), 6.38 (d, 1H, J = 9.0 Hz), 6.59-6.63 (m, 1H), 6.74 (app t, 1H, J = 6.0 Hz), 7.00-7.08 (m, 2H), 7.14-7.19 (m, 1H), 7.45-7.61 (m, 2H), 7.73 (t, 1H, J = 7.2 Hz), 7.81 (d, 1H, J = 7.8 Hz), 8.03-8.11 (m, 2H). APCI, *m/z* = 561 (M+1). LC/MS t_R = 2.81 min.

Synthesis of N^2-{4-Chloro-6-[(3-fluorophenyl)amino]pyrimidin-2-yl}-N^1-(tetrahydrofuran-2-ylmethyl)-L-leucinamide (102e).

To a cold (-15° C), stirred solution of *N*-{4-chloro-6-[(3-fluorophenyl)amino]pyrimidin-2-yl}-L-leucine (0.460 g, 1.3 mmol) in CH_2Cl_2/DMF (5 mL/1mL) was added N-methyl morpholine (0.158 mL, 1.43 mmol) followed by isobutyl chloroformate (0.188 mL, 1.43 mmol). After five minutes, tetrahydrofurfuryl amine (0.148 mL, 1.43 mmol) was added. The reaction was stirred for 45 minutes, concentrated and then chromatographed (SiO_2, CH_2Cl_2/2N NH_3 in MeOH, gradient, 100/0 to 95/5) to give the title compound **102e** as a white solid (0.350 g, 61%). APCI, *m/z* = 436 (M+1). LC/MS t_R = 2.68 min.

Synthesis of *N*-{4-Chloro-6-[(3-fluorophenyl)amino]pyrimidin-2-yl}-L-leucine.

To a solution of methyl *N*-{4-chloro-6-[(3-fluorophenyl)amino]pyrimidin-2-yl}-L-leucinate **102d** (0.5 g, 1.36 mmol) in MeOH (0.5 mL) and THF (2 mL) was added 1 N NaOH (2 mL). The reaction was stirred for one hour, quenched with 1 N HCl (2 mL) and then extracted into CH_2Cl_2 (15 mL). The organic layer was washed with NaCl (sat.) and dried over Na_2SO_4. After removal of the solvent, the title compound was obtained as a white solid (0.47 g, 100%). APCI, *m/z* = 353 (M+1). LC/MS t_R = 2.79 min.

Synthesis of Methyl *N*-{4-chloro-6-[(3-fluorophenyl)amino]pyrimidin-2-yl}-L-leucinate (102d).

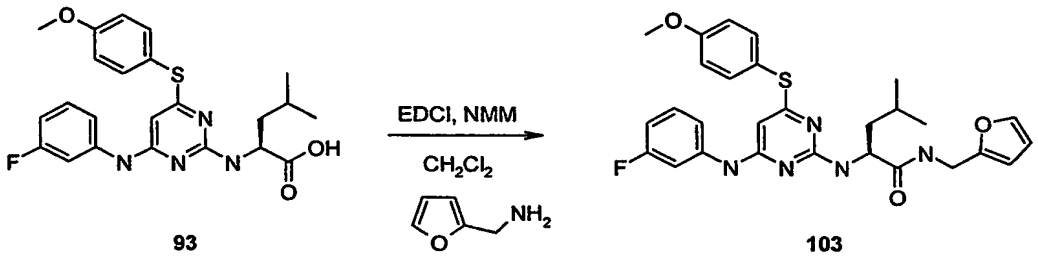
To a solution of 2,6-dichloro-*N*-(3-fluorophenyl)pyrimidin-4-amine **102b** (1.0 g, 3.89 mmol) in i-PrOH (30 mL) was added leucine methyl ester hydrochloride (2.84 g, 15.5 mmol) and DIEA (22.2 mL, 124 mmol) and the reaction heated at reflux for 72 hours. The reaction was concentrated, extracted into CH_2Cl_2 (100 mL) and washed with 1 N HCl (3 x 100 mL). The organic layer was washed with NaCl (sat.), dried over Na_2SO_4 and the volatiles removed to give a white foam (1.0 g, 70%).

Synthesis of 2,6-Dichloro-*N*-(3-fluorophenyl)pyrimidin-4-amine (102b).

To a solution of 2,4,6- trichloropyrimidmine **91a** (2.0 g, 10.9 mmol) in THF (30 mL) was added 3-fluoroaniline (1.04 mL, 10.9 mmol) and the reaction refluxed for 3h. The reaction was concentrated to give a crude mixture of the two isomers in a 3:1 yield. The residual oil

was chromatographed (hexanes/ethyl acetate, gradient, 100/0 to 90/10) to give the title compound as a colorless solid (2.0 g, 71%).

Example 103. N^2-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-(2-furylmethyl)-L-leucinamide (103).



93 103

To a cold (-15° C), stirred solution of *N*-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-leucine **93** (0.050 g, 0.10 mmol) in CH_2Cl_2 (3 mL) was added N-methylmorpholine (0.014 mL, 0.12 mmol), followed by EDCI (0.024 g, 0.125 mmol). The reaction was stirred for five minutes, and then furfuryl amine was added (0.013 g, 0.13 mmol). The reaction was stirred for one hour and then chromatographed (SiO_2, CH_2Cl_2/ethyl acetate, gradient, 100/0 to 95/5) to give **103** as a white foam (0.051 g, 87%). ^1H NMR (300 MHz, $CDCl_3$, 352 K) δ 0.89 (d, 3H, J = 6H), 0.93 (d, 3H, J = 6.0 Hz), 1.50-1.59 (m, 1H), 1.73-1.85 (m, 2H), 3.83 (s, 3H), 4.30-4.37 (m, 3H), 5.01, (d, 1H, J = 6.3 Hz), 5.57 (s, 1H), 6.11 (d, 1H, J = 3.0 Hz), 6.26 (br m, 1H), 6.31 (br m, 1H), 6.69-6.74 (m, 1H), 6.87-6.90 (m, 1H), 6.73 (d, 2H, J = 8.7 Hz), 7.16 (app dd, 1H, J = 9.0, 14.7 Hz), 7.18-7.27 (m, 1H), 7.45 (d, 2H, J = 8.7 Hz). APCI, *m/z* = 536 (M+1). LC/MS t_R = 2.65 min.

By analogy Examples 104-119 were prepared from *N*-{2-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-4-yl}-L-leucine **93**.

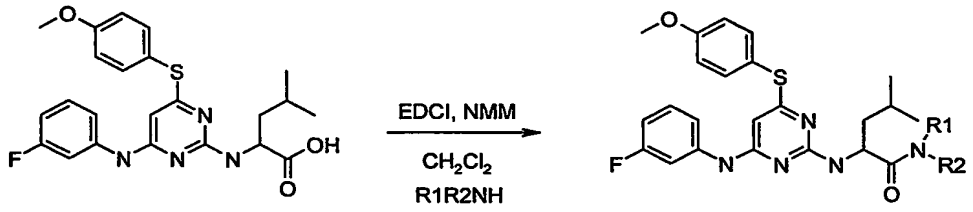


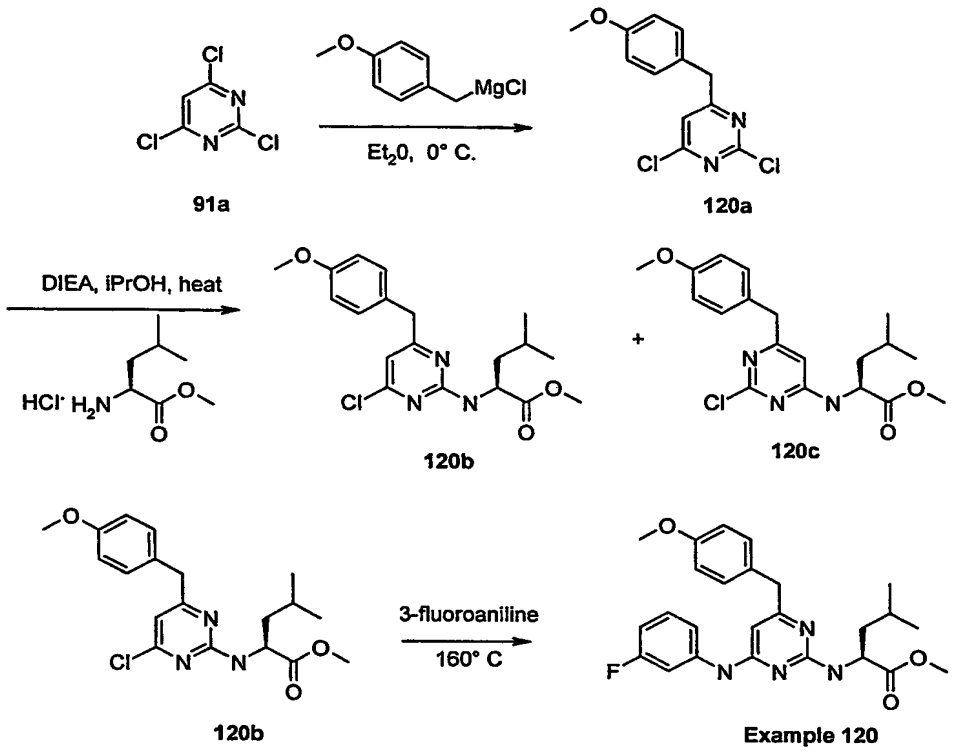
Table 8. Method G, General Procedure for Examples 104-119 and 138.

Example	Name	MS APCI, *m/z* (M+1)	LC/MS t_R (min)
103	N^2-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-(2-furylmethyl)-L-leucinamide	536	2.65
104	N^2-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-(tetrahydrofuran-2-ylmethyl)-L-leucinamide	540	2.61
105	N^2-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-propyl-L-leucinamide	498	2.85
106	N^2-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-(2-morpholin-4-ylethyl)-L-leucinamide	569	2.34
107	N^1-(2,2-Dimethoxyethyl)-N^2-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-L-leucinamide	544	2.55
108	N^2-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-(2-pyridin-2-ylethyl)-L-leucinamide	561	2.29

109	Methyl *N*-{4-[(3-fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-L-leucylglycinate	528	2.50
110	N^2-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-[3-(1*H*-imidazol-1-yl)propyl]-L-leucinamide	564	2.40
111	N^2-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-(2-isopropoxyethyl)-L-leucinamide	542	2.85
112	N^2-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-[2-(methylthio)ethyl]-L-leucinamide	530	2.80
113	N^2-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-pentyl-L-leucinamide	526	3.03
114	*N*-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-L-leucylglycine	514	2.49
115	N^2-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-[2-(1*H*-imidazol-5-yl)ethyl]-L-leucinamide	550	2.55

116	N^2-{4-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-2-yl}-N^1-methoxy-N^1-methyl-L-leucinamide	500	2.95
117	N^2-{2-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-4-yl}-N^1-(2-morpholin-4-ylethyl)-L-leucinamide	569	2.68
118	N^2-{2-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-4-yl}-N^1-(tetrahydrofuran-2-ylmethyl)-L-leucinamide	540	2.95
119	N^2-{2-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-4-yl}-N^1-propyl-L-leucinamide	498	3.01
138	N^2-{2-[(3-Fluorophenyl)amino]-6-[(4-methoxyphenyl)thio]pyrimidin-4-yl}-N^1-1-morpholin-4-yl-L-leucinamide	526	2.80

Example 120. Methyl *N*-[4-[(3-fluorophenyl)amino]-6-(4-methoxybenzyl)pyrimidin-2-yl]-L-leucinate (120).



A stirred solution of methyl *N*-[4-chloro-6-(4-methoxybenzyl)pyrimidin-2-yl]-L-leucinate (0.300 g, 0.70 mmol) **120b** was dissolved in 3-fluoroaniline (0.500 mL) and heated to 160° C for 1 hour. The reaction was cooled and chromatographed (SiO_2, $CHCl_3$/MeOH, gradient, 100/0 to 98/2) to give the title compound **120** as a white foam (0.080 g, 22%). ^{1}H NMR (300 MHz, $CDCl_3$, 300K) δ 0.87 (d, 3H, J = 6.0 Hz), 0.91 (d, 3H, J = 6.0 Hz), 1.61-1.80 (m, 3H), 3.63 (s, 3H), 3.66 (s, 3H), 3.70 (s, 2H), 4.51 (app t, 1H, J = 6.3 Hz), 6.60-6.65 (m, 1H), 6.73 (d, 2H, J = 8.4 Hz), 6.79 (dd, 1H, J = 1.5, 8.1 Hz), 7.15-7.20 (m, 3H), 7.36-7.41 (m, 1H), 7.59 (d, 1H, J = 10.8 Hz), 10.39 (br s, 1H). APCI, *m/z* = 453 (M+1). LC/MS t_R = 2.50 min.

Synthesis of *N*-[4-Chloro-6-(4-methoxybenzyl)pyrimidin-2-yl]-L-leucinate (120b) and methyl *N*-[2-chloro-6-(4-methoxybenzyl)pyrimidin-4-yl]-L-leucinate (120c).

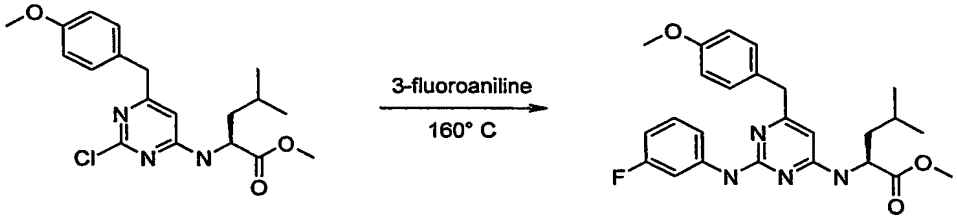
To a solution of 2,4-dichloro-6-(4-methoxybenzyl)pyrimidine **120a** (1.92 g, 7.1 mmol) in iPrOH (15 mL).was added leucine methyl ester hydrochloride (1.29 g, 7.1 mmol) and DIEA (2.49 mL, 14.2 mmol) and the reaction heated to 80° C for 18 hours. The resultant 1:1 mixture of *N*-[4-chloro-6-(4-methoxybenzyl)pyrimidin-2-yl]-L-leucinate **120b** and methyl *N*-[2-chloro-6-(4-methoxybenzyl)pyrimidin-4-yl]-L-leucinate **120c** was concentrated and then chromatographed (SiO_2, hexanes/ethyl acetate, gradient, 100/0 to 0/100

over 38 minutes at 85 ml/min) to give the title compound as a white foam. The material was assigned based on NOE studies. **120b**: ^{1}H NMR (300 MHz, $CDCl_3$, 300K) δ 0.93-1.02 (m, 6H), 1.57-1.79 (m, 3H), 3.71 (s, 3H), 3.79 (br s, 5H), 4.65-4.79 (m, 1H), 5.47 (d, 1H, J = 7.2 Hz), 6.37 (s, 1H), 6.85 (d, 2H, J = 8.7 Hz), 7.14 (d, 2H, J = 8.7 Hz). **102c**: ^{1}H NMR (300 MHz, $CDCl_3$, 300K) δ 0.91-0.93 (m, 6H), 1.61-1.72 (m, 3H), 3.72 (s, 3H), 3.80 (s, 3H), 3.84 (s, 2H), 5.19 (br s, 1H), 5.89 (s, 1H), 6.86 (d, 2H, J = 8.7 Hz), 7.14 (d, 2H, J = 8.7 Hz).

Synthesis of 2,4-Dichloro-6-(4-methoxybenzyl)pyrimidine (120a).

To a cold (0 °C), stirred solution of 2,4,6-trichloropyrimidine **91a** (2.00 g, 10.0 mmol) in diethyl ether (50 mL) was slowly added 4-methoxybenzyl magnesium chloride (38.12 mL, 13.0 mmol). The reaction was stirred for 1 hour and then quenched with NH_4Cl (sat.). The reaction was diluted with diethyl ether and then washed with NaCl (sat.). The organic layer was dried ($MgSO_4$), and then concentrated. The residual oil was chromatographed (SiO_2, hexanes/ethyl acetate, gradient, 100/0 to 0/100 over 38 minutes at 85 ml/min) to give the title compound as a colorless oil (2.15 g, 73%).

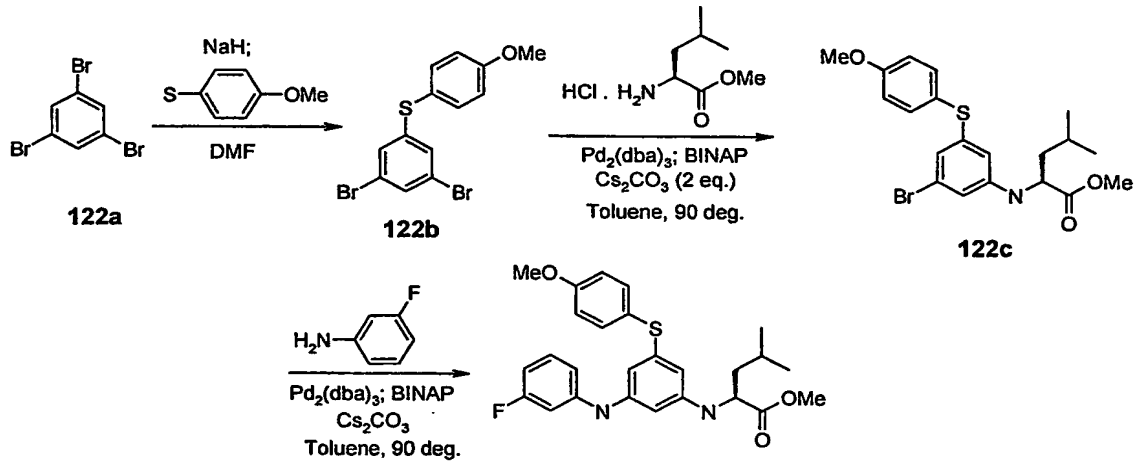
Example 121. Synthesis of Methyl *N*-[2-[(3-fluorophenyl)amino]-6-(4-methoxybenzyl)pyrimidin-4-yl]-L-leucinate (121).



120c **Example 121**

A solution of methyl *N*-[2-chloro-6-(4-methoxybenzyl)pyrimidin-4-yl]-L-leucinate **120c** (0.775 g, 2.05 mmol) in 3-fluoro aniline was heated to 160 °C for 1 hour. The reaction was chromatographed (SiO_2, hexanes/ethyl acetate, gradient, 100/0 to 90/10) to give the title compound **121** as a white foam (0.184 g, 19%). ^{1}H NMR (300 MHz, $CDCl_3$, 300K) δ 0.90 (d, 3H, J = 6.0 Hz), 0.95 (d, 3H, J = 6.0 Hz), 1.63-1.74 (m, 3H), 3.72 (s, 3H), 3.80 (s, 3H), 3.87 (s, 2H), 4.63-4.70 (m, 1H), 5.60-5.68 (m, 2H), 6.79 (app t, 1H, J = 8.4 Hz), 6.88 (d, 2H, J = 8.1 Hz), 7.12-7.29 (m, 4H), 7.59 (d, 1H, J = 11.4 Hz). APCI, *m/z* = 453 (M+1). LC/MS t_R = 2.68 min.

Example 122. (S)-2-[3-(3-Fluoro-phenylamino)-5-(4-methoxy-phenylsulfanyl)-phenylamino]-4-methyl-pentanoic acid methyl ester (122).



Example 122

To a solution of (S)-2-[3-bromo-5-(4-methoxy-phenylsulfanyl)-phenylamino]-4-methyl-pentanoic acid methyl ester **122c** (0.049 g, 0.11 mmol) in toluene (2 mL) was added tris(dibenzylideneacetone)-dipalladium(0) (0.003 g, 0.003 mmol), R(+)-2,2'-bis(diphenylphosphino)-1,1'-binapthyl (0.003 g, 0.005 mmol), cesium carbonate (0.05 g, 0.15 mmol) and 3-fluoroaniline (0.013 g, 0.12 mmol). The solution was heated to 90 °C for 18 h. The toluene was removed *in vacuo* and the residual oil was chromatographed (hexanes/ethyl acetate gradient from 100% to 95% hexane, SiO_2) to give the title compound as a white solid (0.019 g, 36%). ^{1}H NMR (300 MHz, $CDCl_3$, 300K) δ 0.92 (s, 3H, J = 6.3 Hz), 0.93 (s, 3H, J = 6.3 Hz), 1.55 (m, 2H), 1.65-1.78 (m, 1H), 3.68 (s, 3H), 3.82 (s, 3H), 3.95 (app t, 1H, J = 6.9 Hz), 6.02 (s, 1H), 6.09 (s, 1H), 6.18 (s, 1H), 6.55-6.58 (m, 1H), 6.65-6.69 (m, 2H), 6.89 (d, 2H, J = 8.4 Hz), 7.08-7.13 (m, 1H), 7.43 (d, 2H, J = 8.4 Hz). APCI, *m/z* = 469 (M+1). LC/MS t_R = 3.22 min.

1,3-Dibromo-5-(4-methoxy-phenylsulfanyl)-benzene (122b)

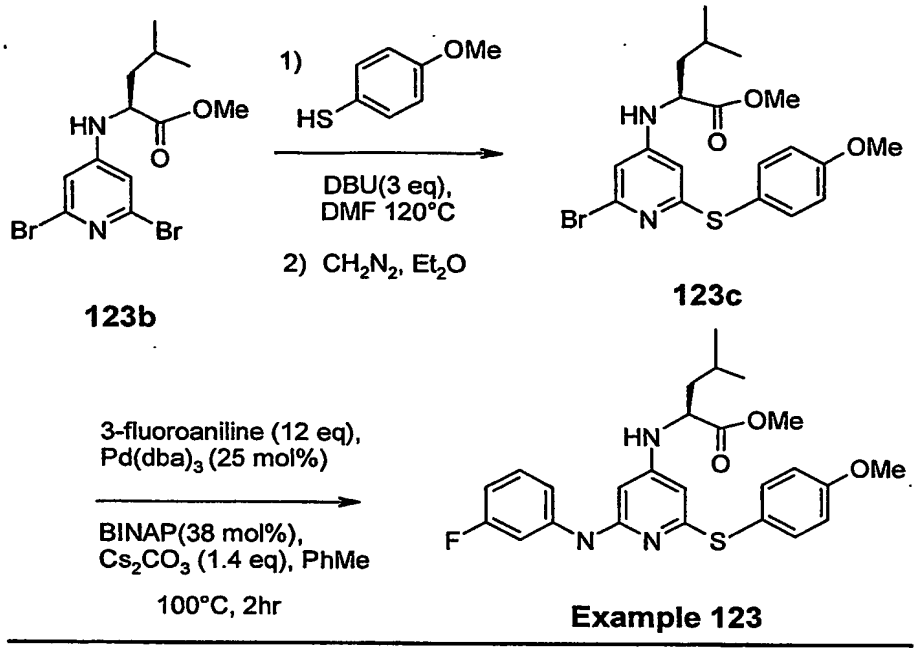
To a cold (0 °C), stirred solution of 1,3,5 tribromobenzene (1.0 g, 3.18 mmol) in DMF was added NaH (117 mg, 60% in mineral oil, 3.49 mmol) and 4-methoxybenzenthiol (0.445 g, 3.18 mmol). The reaction was warmed to room temperature and stirred 2h. To the reaction was added another portion of 4-methoxybenzenethiol (0.445g, 3.18 mmol), followed by potassium tert-butoxide (0.356 g, 3.18 mmol). The reaction was stirred for 24h at which point the mixture was diluted in CH_2Cl_2 (300 mL) and extracted 3 x 100 mL with H_2O and 1 x 100

mL of brine. The organic layer was collected and evaporated to give a yellow oil. This oil was chromatographed (10% EtOAc in hexanes, SiO_2, $R_f = 0.5$) to give 1,3-dibromo-5-(4-methoxy-phenylsulfanyl)-benzene (0.71 g, 60%) **122b**.

(S)-2-[3-Bromo-5-(4-methoxy-phenylsulfanyl)-phenylamino]-4-methyl-pentanoic acid methyl ester (122c)

To a solution of 1,3-dibromo-5-(4-methoxy-phenylsulfanyl)-benzene **122b** (0.200 g, 0.53 mmol) in toluene (5 mL) was added tris(dibenzylideneacetone)-dipalladium(0) (0.014 g, 0.016 mmol), R(+)-2,2'-bis(diphenylphosphino)-1,1'-binapthyl (0.015 g, 0.027 mmol), cesium carbonate (0.487 g, 1.5 mmol) and (S)-leucine methyl ester hydrochloride (0.106 g, 0.58 mmol). The solution was heated at 90 °C for 18 h. An additional portion of tris(dibenzylideneacetone)-dipalladium(0) (0.028 g, 0.032 mmol) and R(+)-2,2'-bis(diphenylphosphino)-1,1'-binapthyl (0.030 g, 0.054 mmol) was added and the reaction heated for another 18 h. The toluene was removed *in vacuo* and the residual oil was chromatographed (hexanes/ethyl acetate gradient from 100% to 95% hexane, SiO_2) to give the title compound as a white solid (0.98 g, 41%). ^{1}H NMR (300 MHz, $CDCl_3$, 300K) δ 0.92 (d, 3H, J = 5.7 Hz), 0.95 (d, 3H, J = 5.7 Hz), 1.50-1.54 (m, 2H), 1.61-1.67 (m, 1H), 3.69 (s, 3H), 3.83 (s, 3H), 3.94 (app t, 1H, J = 6.3 Hz), 6.24 (d, 1H, J = 1.8 Hz), 6.48 (d, 1H, J = 1.8 Hz), 6.58 (d, 1H, J = 1.8 Hz), 6.90 (d, 2H, J = 6.9 Hz), 7.40 (d, 2H, J = 6.9 Hz). APCI, *m/z* = 440, 441(M+1). LC/MS t_R = 3.26 min.

Example 123. (S)-2-[2-(3-Fluoro-phenylamino)-6-(4-methoxy-phenylsulfanyl)-pyridin-4-ylamino]-4-methyl-pentanoic acid methyl ester (123).



Example 123

To a solution of (S)-2-[2-bromo-6-(4-methoxy-phenylsulfanyl)-pyridin-4-ylamino]-4-methyl-pentanoic acid methyl ester **123c** (0.02 g, 0.04 mmol) in toluene (2 mL) was added tris(dibenzylideneacetone)-dipalladium(0) (0.010 g), R(+)-2,2'-bis(diphenylphosphino)-1,1'-binapthyl (0.01 g,), cesium carbonate (0.02 g, 0.06 mmol) and 3-fluoroaniline (0.052 g, 0.04 mmol). The solution was heated at reflux for 2 h. The toluene was removed *in vacuo* and the residual oil was chromatographed (hexanes/ethyl acetate gradient from 100% to 95% hexane, SiO_2) to give the title compound as a white solid (0.05 g, 23%). ^{1}H NMR (300 MHz, $CDCl_3$, 300K) δ 0.80 (d, 3H, J = 6.3 Hz), 0.85 (d, 3H, J = 6.3 Hz), 1.41-1.55 (m, 3H), 3.62 (s, 3H), 3.79 (s, 1H), 5.5 (s, 1H), 5.65 (s, 1H), 6.26 (s, 1H), 6.57 (app t, 1H, J = 10.5 Hz), 6.80 (d, 1H, J = 8.1 Hz), 6.88 (d, 2H, J = 8.7 Hz), 6.95-6.98 (m, 1H), 7.05-7.10 (m, 1H), 7.45 (d, 2H, J = 8.7 Hz). APCI, *m/z* = 470 (M+1). LC/MS t_R = 2.62 min.

Synthesis of (S)-2-[2-Bromo-6-(4-methoxy-phenylsulfanyl)-pyridin-4-ylamino]-4-methyl-pentanoic acid methyl ester (123c).

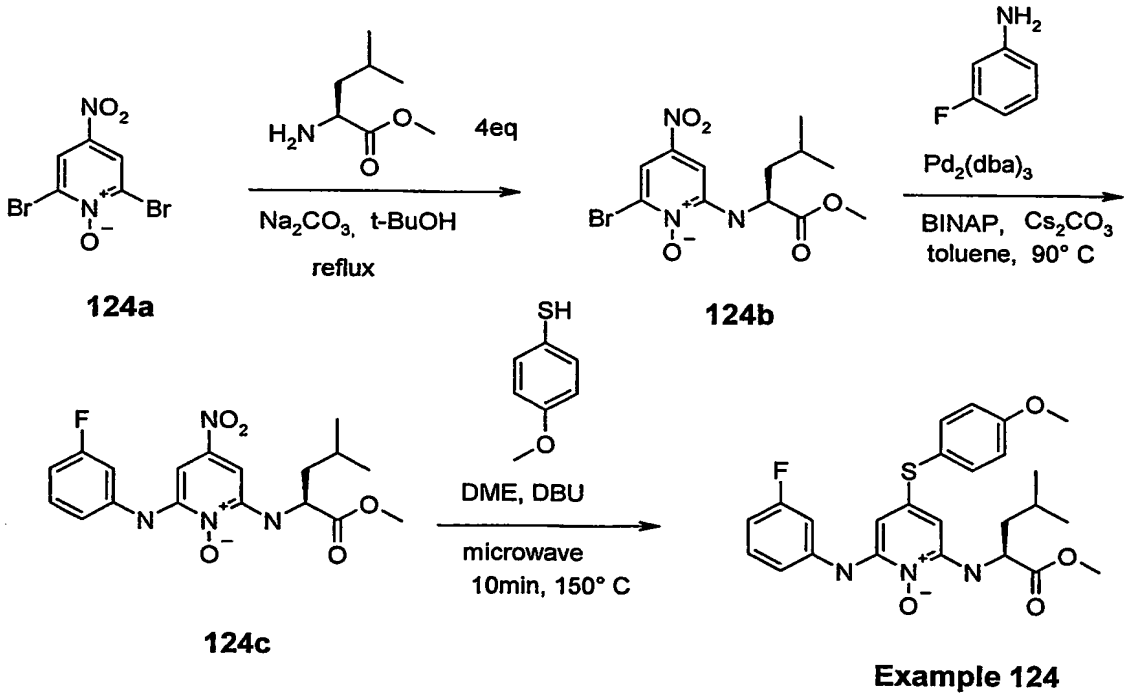
To a solution of (S)-2-(2,6-dibromo-pyridin-4-ylamino)-4-methyl-pentanoic acid methyl ester **123b** (0.126 g, 0.3 mmol) in DMF (1 mL) was added 1,8-diazobicyclo[5.4.0]undec-7-ene (0.19 g, 1.2 mmol) and 4-methoxybenzenethiol (0.17 g, 1.2 mmol). The reaction was heated to 110 °C for 18 h. The mixture was partitioned between ethyl acetate and 1 N HCl. The organic layer was collected and chromatographed using CH_2Cl_2 (SiO_2) to give a mixture of

the ester and acid. The mixture was taken up in ether and esterified using diazomethane (generated from N-methyl-N—nitro-N-nitrosoguanidine, 0.10 g, and 40 % KOH). The reaction was chromatographed (95% hexanes/5%EtOAc, SiO_2) to give the title compound (0.02 g).

Synthesis of (S)-2-(2,6-Dibromo-pyridin-4-ylamino)-4-methyl-pentanoic acid methyl ester:

To a solution of 2,6-dibromo-4-nitro pyridine (1.24 g, 4.3 mmol) (Chem. Ber, 122, 589) in 2-propanol (40 mL) was added (S)-leucine methyl ester hydrochloride (2.4 g, 13.1 mmol) and diisopropylethylamine (3.39 g, 26.3 mmol). The reaction was refluxed overnight, cooled and the solvent removed in vacuo. The residual oil was chromatographed (15% hexane in diethyl ether) to give the title compound as a white solid (0.64 g, 38%) and also (S)-2-(6-bromo-4-nitro-pyridin-2-ylamino)-4-methyl-pentanoic acid methyl ester as a side product (0.18 g, 10%).

Example 124. (S)-2-[6-(3-Fluoro-phenylamino)-4-(4-methoxy-phenylsulfanyl)-1-oxy-pyridin-2-ylamino]-4-methyl-pentanoic acid methyl ester (124).



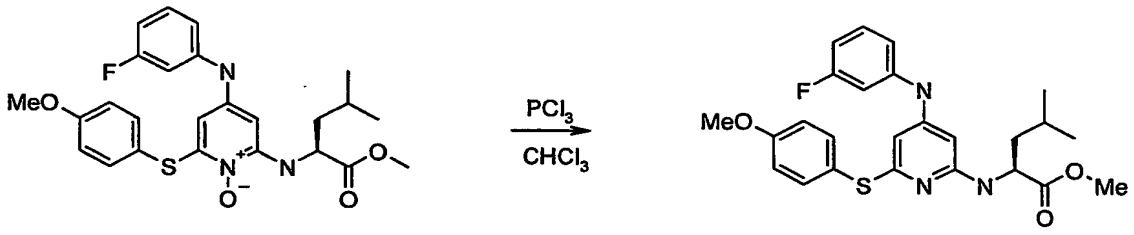
To a solution of (S)-2-[6-(3-fluoro-phenylamino)-4-nitro-1-oxy-pyridin-2-ylamino]-4-methyl-pentanoic acid methyl ester **124c** (0.02 g, 0.05 mmol) in DME was added DBU (0.015 mL,

0.1 mmol) and 4-methoxybenzenethiol (0.013 mL, 0.1 mmol). The reaction was heated to 150 °C for five minutes in a Personal Chemistry Smithsynthesizer. The reaction was concentrated and chromatographed (95/5 CH_2Cl_2/MeOH) to give a white solid (0.024 g, 100%). ^{1}H NMR (300 MHz, $CDCl_3$, 300K) δ 0.93 (d, 3H, J = 6.0 Hz), 0.96 (d, 3H, J = 6.0 Hz), 1.72-1.83 (m, 3H), 3.69 (s, 3H), 3.84 (s, 3H), 3.84-3.99 (m, 1H), 5.64 (d, 1H, J = 2.1 Hz), 6.06 (d, 1H, J = 2.1 Hz), 6.70-6.80 (m, 3H), 6.85 (d, 1H, J = 8.7 Hz), 6.95 (d, 2H, J = 8.7 Hz), 7.19-7.22 (m, 1H), 7.45 (d, 2H, J = 8.7 Hz), 8.65 (s, 1H). APCI, *m/z* = 486 (M+1). LC/MS t_R = 2.78 min.

Preparation of (S)-2-[6-(3-fluoro-phenylamino)-4-nitro-1-oxy-pyridin-2-ylamino]-4-methyl-pentanoic acid methyl ester (124c)

A solution of 2,5-dibromo-4-nitro-pyridyl-N-oxide **124a** (1 mmol) was refluxed in tert-butyl alcohol with Na_2CO_3 (8 mmol) and (S)-leucine methyl ester hydrochloride (4 mmol). After 24 h at reflux the reaction was cooled and the residual material chromatographed (CH_2Cl_2/MeOH gradient, SiO2) to give the intermediate mono-bromide. A portion of this compound **124b** (0.5 mmol) was converted to the title compound using the general palladium mediated coupling method described for Example 126 (utilizing 3-fluoroaniline as the amine).

Example 125. (S)-2-[4-(3-Fluoro-phenylamino)-6-(4-methoxy-phenylsulfanyl)-pyridin-2-ylamino]-4-methyl-pentanoic acid methyl ester (125)

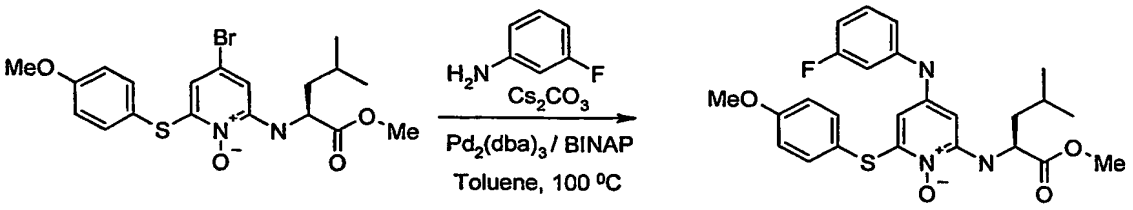


Example 126 **Example 125**

A solution of (S)-2-[4-(3-fluoro-phenylamino)-6-(4-methoxy-phenylsulfanyl)-1-oxy-pyridin-2-ylamino]-4-methyl-pentanoic acid methyl ester **126** (0.054 g, 0.11 mmol) in $CHCl_3$ was treated with 3-fluoroaniline (27 uL) and then PCl_3 (3 x 9.3 uL, 0.32 mmol). The reaction was stirred for 1.5 hours and then the volatiles removed *in vacuo*. The residual material was partitioned between ethyl acetate and $NaHCO_3$ (sat.). The organic layer was dried over Na_2SO_4, and concentrated. Column chromatography ($CHCl_3$, SiO_2) gave the desired material (0.037 g, 71%). ^{1}H NMR (300 MHz, $CDCl_3$, 300K) δ 0.89-0.95 (m, 6H), 1.54-1.62 (m, 2H), 1.66-1.75 (m, 1H), 3.69 (s, 3H), 3.82 (s, 3H), 4.08-4.15 (m, 1H), 4.39-4.41 (m, 1H), 4.62-4.65

(m, 1H), 5.69 (s, 2H), 5.83 (s, 1H), 6.70-6.75 (m, 3H), 6.90 (d, 2H, J = 9.0 Hz), 7.12-7.20 (m, 1H), 7.50 (d, 2H, J = 9.0 Hz). APCI, *m/z* = 470 (M+1). LC/MS t_R = 2.52 min.

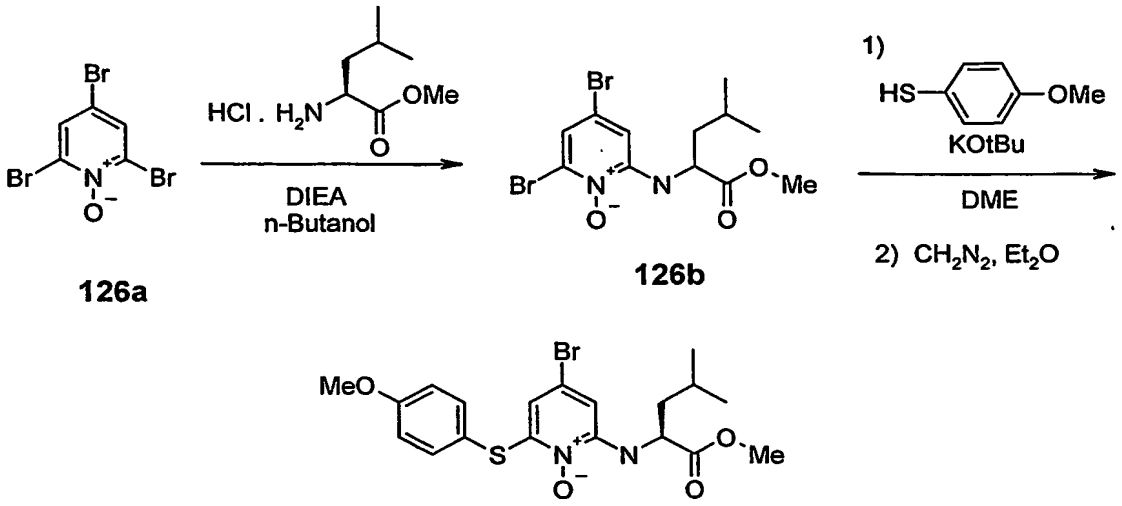
Example 126. (S)-2-[4-(3-Fluoro-phenylamino)-6-(4-methoxy-phenylsulfanyl)-1-oxy-pyridin-2-ylamino]-4-methyl-pentanoic acid methyl ester (126).



126c **Example 126**

To a solution of (S)-2-[4-(3-bromo)-6-(4-methoxy-phenylsulfanyl)-1-oxy-pyridin-2-ylamino]-4-methyl-pentanoic acid methyl ester **126c** (0.100 g, 0.21 mmol) in toluene (1 mL) was added tris(dibenzylideneacetone)-dipalladium(0) (0.006 g, 0.006 mmol), R(+)-2,2'-bis(diphenylphosphino)-1,1'-binapthyl (0.006 g, 0.009 mmol), cesium carbonate (0.100 g, 0.30 mmol) and 3-fluoroaniline (0.029 g, 0.26 mmol). The solution was heated to 90 °C for 1 h. The toluene was removed *in vacuo* and the residual oil was chromatographed ($CHCl_3$/2N NH_3 in MeOH-- gradient from 100% to 98%, SiO_2) to give the title compound as a white solid (0.064 g, 60%). ^{1}H NMR (300 MHz, $CDCl_3$, 300K) δ 0.87 (d, 3H, J = 6.0 Hz), 0.93 (d, 3H, J = 6.0 Hz), 1.73-1.78 (m, 3H), 3.69 (s, 3H), 3.82 (s, 3H), 3.93-4.01 (m, 1H), 5.48 (d, 1H, J = 2.4 Hz), 5.86 (d, 1H, J = 2.4 Hz), 6.51 (br s, 1H), 6.62-6.68 (m, 3H), 6.94 (d, 2H, J = 8.7 Hz), 6.96-6.99 (m, 1H), 7.12-7.17 (m, 1H), 7.39 (d, 2H, J = 8.7 Hz).

Synthesis of (S)-2-[4-(3-Bromo)-6-(4-methoxy-phenylsulfanyl)-1-oxy-pyridin-2-ylamino]-4-methyl-pentanoic acid methyl ester (126c).

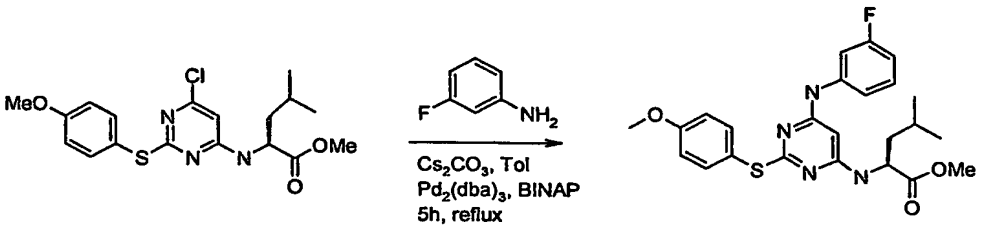


126a 126b 126c

To a solution of 2,4,6-tribromo-pyridyl-N-oxide **126a** (1 mmol) in n-butanol (30 mL) was added L-leucine methyl ester hydrochloride (1 mmol) and diisopropylethylamine (2.5 mmol). The reaction was heated to reflux for 18 h. Upon cooling the volatiles were removed in vacuo and the material chromatographed to give a separable mixture of the desired methyl ester, (S)-2-(4,6-dibromo-1-oxy-pyridin-2-ylamino)-4-methyl-pentanoic acid methyl ester **126b**, and the n-butyl ester.

4-Methoxybenzenthiol (0.147 g, 1.05 mmol) was dissolved in DME (3 mL) and to this was added potassium tert-butoxide (0.117 g, 1.05 mmol), followed by (S)-2-(4,6-dibromo-1-oxy-pyridin-2-ylamino)-4-methyl-pentanoic acid methyl ester **126b** (0.397 g, 0.99 mmol). After one hour, another portion of potassium tert-butoxide (0.117 g, 1.05 mmol) and 4-methoxybenzenethiol (0.397 g, 0.99 mmol) was added and the solution stirred for one hour. The reaction was quenched with 1N HCl (ca. 2mL) and the reaction partitioned between CH_2Cl_2 and H_2O. The organic layers were collected, dried over Na_2SO_4 and concentrated. The entire crude material was treated with CH_2N_2 (as generated from 1.75 mmol of N-methyl-N-nitro-N-nitrosoguanidine and 40% KOH) until all was converted into the methyl ester. The residue was chromatographed ($CHCl_3$/2N NH_3 in MeOH-- gradient from 100% to 98%, SiO_2) to give the title compound as a white solid (0.401 g, 87%).

Example 127. 2-[6-(3-Fluoro-phenylamino)-2-(4-methoxy-phenylsulfanyl)-pyrimidin-4-ylamino]-4-methyl-pentanoic acid methyl ester (127).



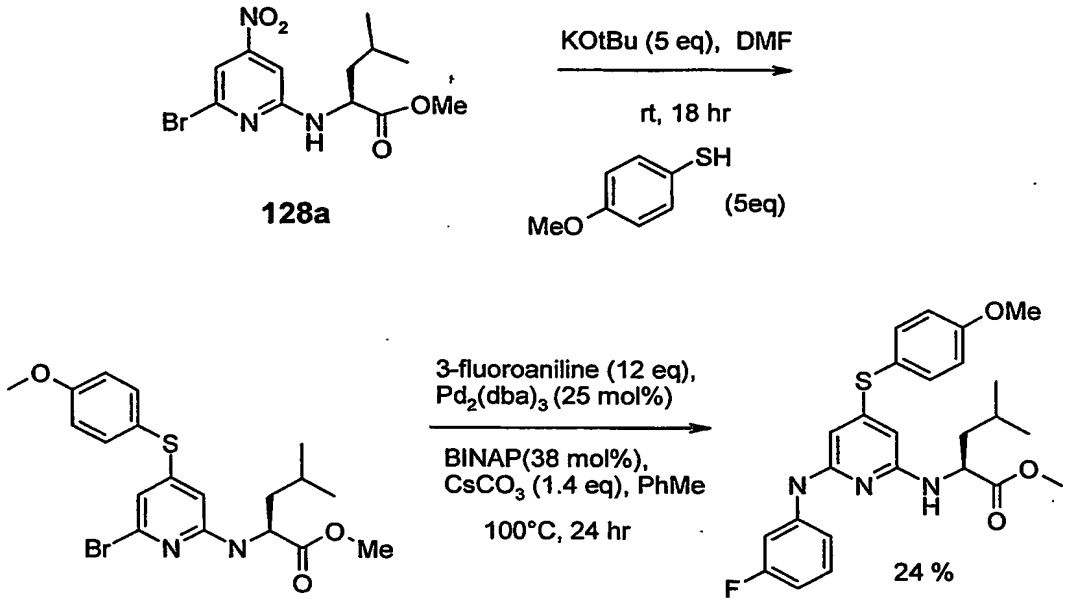
91e **Example 127**

To a stirred solution of methyl *N*-{6-chloro-2-[(4-methoxyphenyl)thio]pyrimidin-4-yl}-L-leucinate **91e** (0.062 g, 0.15 mmol) in toluene (2 mL) was added tris(dibenzylideneacetone)-dipalladium(0) (0.006 g, 0.006 mmol), R(+)-2,2'-bis(diphenylphosphino)-1,1'-binapthyl (0.006 g, 0.009 mmol), cesium carbonate (0.100 g, 0.30 mmol) and 3-fluoroaniline (0.024 g, 0.22 mmol). The solution was heated at 90 °C for 1 h. The toluene was removed *in vacuo* and the residual oil was chromatographed (hexanes/ethyl acetate gradient 100% to 75%, SiO_2) to give the title compound as a white solid (0.024 g, 32%). ^1H NMR (300 MHz, $CDCl_3$, 300K) δ 0.87 (d, 3H, J = 6.3 Hz), 0.90 (d, 3H, J = 6.3 Hz), 1.53-1.70 (m, 3H), 3.69 (s, 3H), 3.85 (s, 3H), 4.39 (br s, 1H), 4.83-4.86 (m, 1H), 5.42 (s, 1H), 6.35 (s, 1H), 6.70 (ddd, 1H, J = 1.8 Hz, 8.4 Hz, 8.5 Hz), 6.83 (d, 1H, J = 7.8 Hz), 6.92 (d, 2H, J = 8.7 Hz), 7.16 (dd, 1H, J = 6.6 Hz, 14.7 Hz), 7.52 (d, 2H, J = 8.7 Hz). APCI, *m/z* = 471 (M+1). LC/MS t_R = 2.80 min.

Synthesis of Methyl *N*-{6-chloro-2-[(4-methoxyphenyl)thio]pyrimidin-4-yl}-L-leucinate (91e)

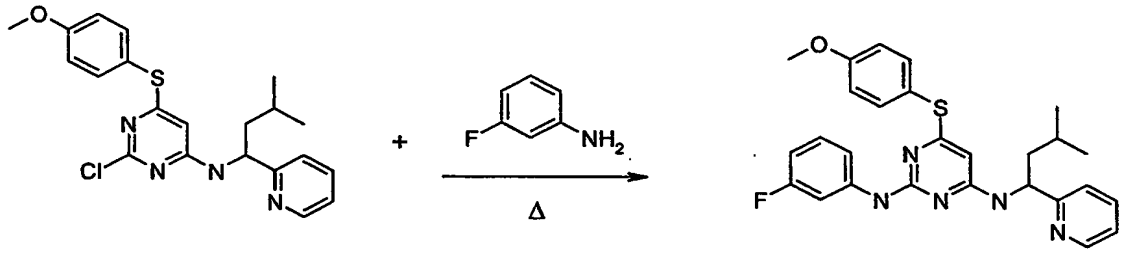
Preparation of **91e** is described in example 91. The title compound was separated from isomer **91d** by chromatography (hexanes/ethyl acetate gradient 90/10 to 80/20, SiO_2).

Example 128. (S)-2-[6-(3-fluoro-phenylamino)-4-(4-methoxy-phenylsulfanyl)-pyridin-2-ylamino]-4-methyl-pentanoic acid methyl ester (128).



Example **128** was prepared in analogy to Example **122**, beginning with (S)-2-[6-bromo-4-(4-methoxy-phenylsulfanyl)-pyridin-2-ylamino]-4-methyl-pentanoic acid methyl ester **128b** as the starting material. Column chromatography (CH_2Cl_2, SiO_2) gave the title compound as a white solid (12%).

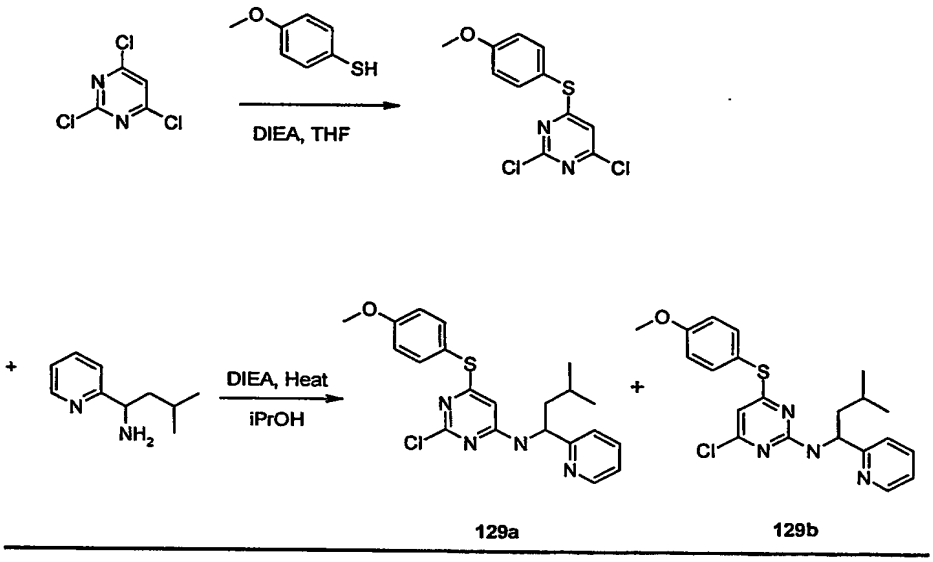
Example 129. N^2-(3-Fluoro-phenyl)-6-(4-methoxy-phenylsulfanyl)-N^4-(3-methyl-1-pyridin-2-yl-butyl)-pyrimidine-2,4-diamine (129).



To [2-chloro-6-(4-methoxy-phenylsulfanyl)-pyrimidin-4-yl]-(3-methyl-1-pyridin-2-yl-butyl)-amine **129a** (0.110 g, 0.2 mmol) was added 3-fluoroaniline (0.1 mL) and the reaction was heated to 150 °C for 10 minutes. The reaction was cooled and chromatographed (hexanes/ethyl acetate gradient 90/10 to 80/20, SiO_2) to give the title compound as a white solid (0.034 g, 28%). ^{1}H NMR (300 MHz, $CDCl_3$, 300K) δ 0.87 (d, 3H, J = 6.3 Hz), 0.95 (d,

3H, J = 6.3 Hz), 1.65-1.70 (m, 3H), 3.86 (s, 3H), 5.29 (s, 1H), 5.38-5.41 (m, 1H), 6.63-6.65 (m, 1H), 6.82 (s, 1H), 6.92-6.98 (m, 3H), 7.10-7.20 (m, 3H), 7.46 (d, 2H, J = 8.7 Hz), 7.57-7.61 (m, 2H), 8.52 (d, 1H, J = 4.2 Hz). APCI, *m/z* = 490 (M+1). LC/MS t_R = 2.46 min.

Synthesis of [2-chloro-6-(4-methoxy-phenylsulfanyl)-pyrimidin-4-yl]-(3-methyl-1-pyridin-2-yl-butyl)-amine 129a and [4-Chloro-6-(4-methoxy-phenylsulfanyl)-pyrimidin-2-yl]-(3-methyl-1-pyridin-2-yl-butyl)-amine 129b

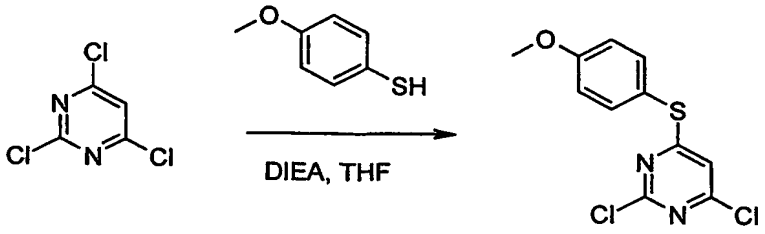


To a stirred solution of 2,4-dichloro-6-(4-methoxy-phenylsulfanyl)-pyrimidine (1.22 g, 4.23 mmol) in isopropyl alcohol was added 3-methyl-1-pyridin-2-yl-butylamine (0.840 g, 5.1 mmol) and diisopropylethylamine (0.91 mL, 5.1 mmol) and the reaction heated to reflux for 3 h. The reaction was cooled and chromatographed (hexanes/ethyl acetate 80/20, SiO_2) to give the two isomers as white solids (regiochemical isomers were established using NOE spectroscopy):

129a: ^{1}H NMR (300 MHz, $CDCl_3$, 300K) δ 0.80-0.85 (m, 6H), 1.45-1.59 (m, 3H), 3.87 (s, 3H), 5.42-5.45 (m, 1H), 5.84-5.86 (m, 1H), 6.92-6.97 (m, 3H), 7.13-7.17 (m, 1H), 7.39-7.42 (m, 2H), 7.58-7.62 (m, 1H), 8.45 (d, 1H, J = 4.2 Hz). APCI, *m/z* = 415 (M+1). LC/MS t_R = 2.28 min.

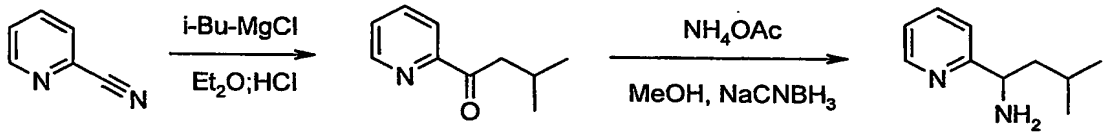
129b: ^{1}H NMR (300 MHz, $CDCl_3$, 300K) δ 0.91-0.92 (m, 6H), 1.68-1.70 (m, 3H), 3.86 (s, 3H), 5.10 (br s, 1H), 5.96-5.99 (m, 2H), 6.96 (d, 2H, J = 8.6 Hz), 7.11-7.15 (m, 1H), 7.46 (d, 2H, 8.6 Hz), 8.54 (d, 1H, J = 3.0 Hz). APCI, *m/z* = 415 (M+1). LC/MS t_R = 2.34 min.

Synthesis of 2,4-dichloro-6-(4-methoxy-phenylsulfanyl)-pyrimidine



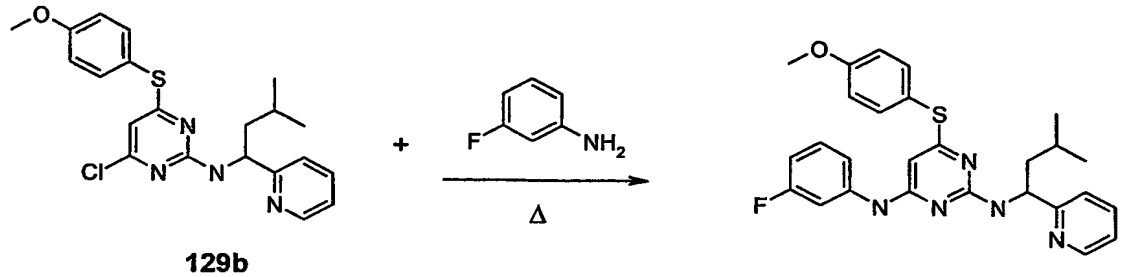
To a cold (0 °C) solution of 2,4,6-trichloropyrimidine (2.24 g, 12.2 mmol) in THF was added 4-methoxybenzenethiol (1.73 g, 12.2 mmol), followed by diisopropylethylamine (2.23 mL, 12.5 mmol). The reaction was warmed to room temperature and the solvent removed *in vacuo*. The residual oil was partitioned between CH_2Cl_2 and 1N HCl, and the organic layer was collected. The CH_2Cl_2 layer was dried (Na_2SO_4) and then the solvent removed to give the title compound as a colorless oil. The material was used in the next reaction without further purification.

Synthesis of -methyl-1-pyridin-2-yl-butylamine



To a solution of 2-cyanopyridine (2.0 g, 19.2 mmol) in diethylether was added isobutyl magnesium bromide (9.6 mL) and the reaction was stirred for 1 h. The reaction was quenched with 1N HCl. The ether layer was separated and dried with NaCl (sat.) and Na_2SO_4. The solvent was evaporated to give the ketone intermediate. The ketone was dissolved in MeOH and to this was added NH_4OAc (2.3 g, 6.1 mmol) and $NaCNBH_3$ (0.46 g, 7.3 mmol). The reaction was refluxed for 3h, and the solvent removed *in vacuo*. The residual oil was partitioned between diethyl ether and 1 N HCl. The acid layer was collected and washed with ether. The aqueous layer was treated with 10 N NaOH until the solution was basic. The aqueous layer was then extracted with ether and the ether layer was collected. This layer was washed with NaCl (sat.) and dried Na_2SO_4. Removal of solvent gave the title compound as a colorless oil (0.85 g, 25%). The compound was used with no further purification.

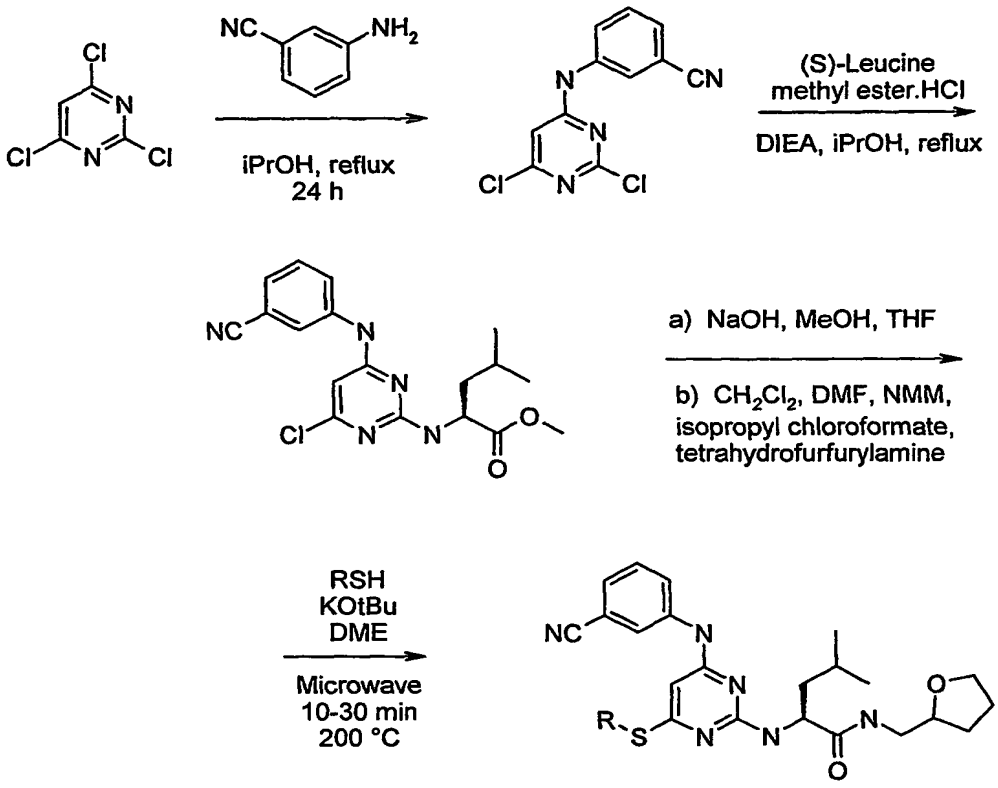
Example 130. N^4-(3-Fluoro-phenyl)-6-(4-methoxy-phenylsulfanyl)-N^2-(3-methyl-1-pyridin-2-yl-butyl)-pyrimidine-2,4-diamine (130).



129b **Example 130**

The title compound was prepared in analogous fashion to Example 128, beginning with [4-chloro-6-(4-methoxy-phenylsulfanyl)-pyrimidin-2-yl]-(3-methyl-1-pyridin-2-yl-butyl)-amine **129b** as the starting pyrimidine. ^{1}H NMR (300 MHz, $CDCl_3$, 300K) δ 0.92-0.95 (m, 6H), 1.71-1.73 (m, 3H), 3.85 (s, 3H), 5.11-5.16 (m, 1H), 5.35 (br s, 1H), 5.67 (br s, 1H), 6.29 (br s, 1H), 6.65-6.70 (m, 1H), 6.84 (d, 1H, J = 9.0 Hz), 6.95 (d, 2H, J = 8.7 Hz), 7.09-7.15 (m, 3H), 7.50 (d, 2H, J = 8.7 Hz), 7.55-7.60 (m, 1H), 8.53-8.56 (m, 1H). APCI, *m/z* = 490 (M+1). LC/MS t_R = 2.40 min.

Synthesis of Examples 131-134:

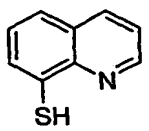
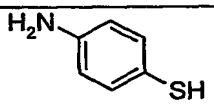
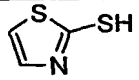
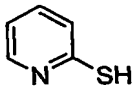


Examples 131-134

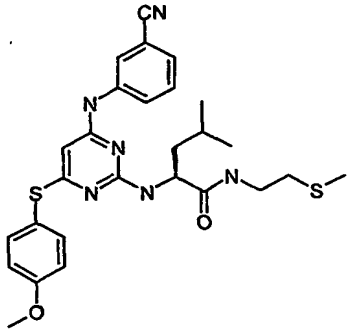
General Procedure (Examples 131-134 were prepared by analogy to example 102): (S)-2-[4-Chloro-6-(3-cyano-phenylamino)-pyrimidin-2-ylamino]-4-methyl-pentanoic acid methyl ester (0.113 mmol) was heated with thiols (0.226 mmol) (as described in Table 9) and potassium tert-butoxide (0.226 mmol) for 10-30 minutes at 200 °C in a Personal Chemistry Smithsynthesizer. Reactions were then purified by column chromatography (99/1 CH_2Cl_2/MeOH, SiO_2).

Synthesis of (S)-2-[4-Chloro-6-(3-cyano-phenylamino)-pyrimidin-2-ylamino]-4-methyl-pentanoic acid methyl ester was prepared by analogy to **102e** in Example 102.

Table 9. Examples 131-134

Example	Starting Thiol	MS (m/z)	HPLC retention time	Name
131		568	2.37	(S)-2-[4-(3-Cyano-phenylamino)-6-(quinolin-8-ylsulfanyl)-pyrimidin-2-ylmethyl]-4-methyl-pentanoic acid (tetrahydro-furan-2-ylmethyl)-amide
132		532	2.28	(S)-2-[4-(4-Amino-phenylsulfanyl)-6-(3-cyano-phenylamino)-pyrimidin-2-ylmethyl]-4-methyl-pentanoic acid (tetrahydro-furan-2-ylmethyl)-amide
133		523	2.44	(S)-2-[4-(3-Cyano-phenylamino)-6-(thiazol-2-ylsulfanyl)-pyrimidin-2-ylmethyl]-4-methyl-pentanoic acid (tetrahydro-furan-2-ylmethyl)-amide
134		517	2.32	(S)-2-[4-(3-Cyano-phenylamino)-6-(pyridin-2-ylsulfanyl)-pyrimidin-2-ylmethyl]-4-methyl-pentanoic acid (tetrahydro-furan-2-ylmethyl)-amide

Example 137. (S)-2-[4-(3-Cyano-phenylamino)-6-(4-methoxy-phenylsulfanyl)-pyrimidin-2-ylmethyl]-4-methyl-pentanoic acid(2-methylsulfanyl-ethyl)-amide (137).



Preparation of the title compound was accomplished by analogy to Examples 131-134, using 2-methylsulfanyl-ethylamine as the amine in the amide-bond coupling reaction, and 3-cyano-aniline in the formation of the di-chloropyrimidine. ^{1}H NMR (300 MHz, $CDCl_3$, 300K) δ □ 0.90 (d, 3H, J = 6.3 Hz), 0.96 (d, 3H, J = 6.3 Hz), 1.55-1.61 (m, 3H), 2.05 (s, 3H), 2.55 (t, 2H, J = 6.6 Hz), 3.39 (q, 2H, J = 6.3 Hz), 3.87 (s, 3H), 4.34 (br s, 1H), 5.29 (s, 1H), 6.60 (br s, 1H), 7.00 (d, 2H, J = 8.7 Hz), 7.27-7.38 (m, 2H), 7.38-7.60 (m, 2H). APCI, *m/z* = 537 (M+1). LC/MS t_R = 2.63 min.

The compounds of the present invention have utility for the prevention and treatment of Alzheimer's disease by inhibiting amyloid β production. Methods of treatment target formation of amyloid β production through enzymes involved in the proteolytic processing of β amyloid precursor protein. Compounds that inhibit β and γ secretase activity, either directly or indirectly, control the production of amyloid β. The inhibitions of β and γ secretases reduce the production of amyloid β and are thought to reduce or prevent the neurological disorders such as Alzheimer's disease. The compounds of the present invention have utility for the prevention and treatment of disorders involving amyloid β production, such as cerebrovascular disorders.

Compounds described herein have been shown to inhibit amyloid β production, as determined by the gamma secretase detergent extract assay with IC_{50} activity ranging from 0.010 uM to 5.50 uM and gamma secretase whole cell assay with IC_{50} activity ranging from 0.10 uM to 12.0 uM. These assays are described below.

Compounds provided by this invention should also be useful as standards and reagents in determining the ability of a potential pharmaceutical to inhibit amyloid β production. These would be provided in commercial kits comprising a compound of this invention.

As used herein "ug " denotes microgram, "mg" denotes milligram, "g" denotes gram, "uL" denotes microliter, "mL" denotes milliliter, "L" denotes liter, "nM" denotes nanomolar, ".uM" denotes micromolar, "mM" denotes millimolar, "M" denotes molar, "nm" denotes nanometer, "DMSO" denotes dimethyl sulfoxide, "DTT" denotes dithiothreitol, "DPBS" denotes "EDTA" denotes ethylenediaminetetraacetate,

Gamma Secretase Detergent Extract Assay

The gamma secretase enzyme assay measures the amount of amyloid β (Aβ)40 product generated by the cleavage of C100, a truncated form of amyloid precursor protein (APP). The C100 substrate is a recombinant protein purified from *E. coli* inclusion bodies. The γsecretase enzyme complex is prepared by detergent extraction of HeLa 8A8 cell membranes. The enzyme reaction contains 10 ul of inhibitor at a defined concentration, diluted from a DMSO stock into 96-well microplates (final concentration of DMSO is maintained at 5%). 20 ul of the C100 substrate (600 nM final concentration), in reaction buffer, (50 mM MES, pH 6.5, containing 100 mM NaCl, 1 mM EDTA, 1 mM DTT, 1 mg/mL BSA, 0.25% Chapso, 0.01% PE, 0.01% PC and a protease cocktail), is added to the plates. The reactions are initiated by addition of 10ul enzyme at a 20-fold dilution from stock. An Aβ40 standard curve diluted in the reaction buffer plus C100 is included in each assay. Plates are incubated for 3 hours at 37 degrees. After the incubation period, 50 ul of an antibody mixture is added: rabbit anti-Aβ40 antibody (Biosource #44-3481) at 0.16 ug/ml and biotinylated 4G8 (Senetek #240-10) at 0.25 ug/ml in DPBS (Fisher # MT21031CV) containing 0.5% bovine serum albumin, 0.5% Tween 20. Plates are then incubated overnight at 4 degrees. The following morning, a 50 ul mixture of 0.0625 mg/ml Ruthenium labeled goat anti-rabbit IgG (labeled in-house) and 125 ug/ml of Streptavadin beads (Igen #M280), diluted in the same DPBS buffer, is added to detect the cleaved product. After a one hour incubation period at room temperature, an Igen M Series instrument is utilized to quantitate the results by electrochemiluminescence.

Gamma Secretase Whole Cell Assay (GSWC)

Preparation of cells for assay

Human Embryonic Kidney (HEK) cells stably expressing human Amyloid Precursor protein (APP) and Presenelin I were grown in DMEM media (Fisher MT10013CV) containing 10% fetal calf serum (Fisher #MT135011CV), 0.2 mg/mL G418 (Fisher #MT30234CR) and 1X concentration of antibiotic/antimycotic mixture (Fisher #MT30004CI). Cells were grown in tissue culture flasks and passaged every week at a ratio of 1:30.

Thirty minutes prior to incubation with test compounds, cells were harvested by treating the monolayer with DPBS (Fisher #MT21031CV) containing 3 mM EDTA. Cells were resuspended at a density of 2 million cells/mL in complete growth medium.

Test compounds were solubilized in DMSO at a concentration of 3.3 mM. From this stock solution a dilution series was prepared in complete growth medium of cells. Dilution series were then transferred to 96 well assay plate (Costar #3595) with 100 uL in each well. Cells (100 uL) were added to each well containing test compound. Two controls, one containing only cells (Total) and one containing only growth medium (Background) were also included. Cells were incubated with compounds for 14-16 hours in cell culture incubator.

At the end of 14-16 hour incubation, 100 uL of supernatant was transferred from each well in to a polypropylene 96 well plate. This supernatant was mixed with 100 u L of DPBS (Fisher # MT21031CV) containing 0.5% bovine serum albumin, 0.5% Tween (or an equivalent) 20, 0.25 u g/mL of biotinylated 4G8 (Senetek #240-10), 0.18 u g/mL rabbit anti-Aβ40 antibody (Biosource #44-3481), 0.045 ug/mL Ruthenium labeled goat anti-rabbit IgG (labeled in-house) and 60 ug/mL of Streptavadin beads (Igen #M280). The mixture was incubated for 4-6 hours at 4 °C on a plate shaker.

At the completion of 4-6 hour incubation, plate was brought to room temperature and the generated Aβ40 was detected using the Igen M8 analyzer. Raw data was imported into Microsoft Excel software. IC_{50} values for inhibition of Aβ 40 generation by test compounds were calculated using Excel-Fit.